



ODAC Sponsor Briefing Book

Drug Substance Olaparib (AZD2281)

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**OLAPARIB MONOTHERAPY AS MAINTENANCE TREATMENT OF
PATIENTS WITH PLATINUM-SENSITIVE RELAPSED GERMLINE
BRCA MUTATED (*gBRCAm*) OVARIAN CANCER**

SPONSOR BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ACMG	American College of Medical Genetics and Genomics
AE	Adverse event
AML	Acute myeloid leukemia
AP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AT	Aminotransferase
AUC	Area under plasma concentration-time curve
AUC _{ss}	Area under plasma concentration-time curve at steady state
AZD2281	The generic name olaparib is generally used when referring to the drug substance known by the laboratory code AZD2281 or KU-0059436
BART	BRCA _{Analysis} Rearrangement Test
BCRP	Breast cancer resistance protein
bd	Twice daily
BIC	Breast Cancer Information Core
BICR	Blinded independent central review
<i>BRCA</i>	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicized whereas protein is not italicized).
<i>BRCA_m</i>	<i>BRCA</i> mutated
<i>BRCA_{wt/VUS}</i>	<i>BRCA</i> wildtype/variant of unknown significance
CA-125	Cancer antigen (CA)-125 (tumor biomarker)
CAP	College of American Pathologists
CEDR	Center for Drug Evaluation and Research
CDRH	Center for Device and Radiological Health
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C _{max}	Maximum plasma concentration
C _{max ss}	Maximum plasma concentration at steady state
CMC	Chemistry Manufacturing and Control
CR	Complete response

Abbreviation or special term	Explanation
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCO	Data cut-off
DSBs	(DNA) double-strand breaks
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ENGOT	European Network for Gynecological Oncological Trial groups
FACT-O	Functional Assessment of Cancer Therapy – Ovarian
FOSI	FACT.NCCN ovarian symptom index
FFPE	Formalin fixed paraffin embedded
FTIM	First time in man
<i>gBRCAm</i>	Germline <i>BRCA</i> mutated
<i>gBRCAwt/VUS</i>	Germline <i>BRCA</i> wildtype/variant of unknown significance
hERG	Human ether-a-go-go related gene
HR	Hazard ratio
HRD	Homologous recombination deficient/deficiency
HRQoL	Health-related quality of life
IC ₅₀	Half maximal inhibitory concentration
INR	Prothrombin international normalized ratio
ITT	Intention to treat
KU-0059436	The generic name olaparib is generally used when referring to the drug substance known by the laboratory code AZD2281 or KU-0059436
LDT	Laboratory developed test
LMG	Lauroyl macrogol-32 glycerides
MAA	(European) Marketing Authorization Application
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRP2	Multi-drug resistance protein 2
MTD	Maximum tolerated dose
NC	Not calculated
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NE	Not evaluable
OATP	Organic anion-transporting polypeptide

Abbreviation or special term	Explanation
OCT	Organic cation-transporter
ORR	Objective response rate
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose polymerase
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time from start of randomization to second progression or death
PK	Pharmacokinetic(s)
PLD	Pegylated liposomal doxorubicin
PMA	Pre-Market Approval
PR	Partial response
PS	Performance status
PSR	Platinum-sensitive relapsed
Q	Quarter (eg, 1Q2015 = first calendar quarter of 2015)
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SSBs	(DNA) single-strand breaks
t_{\max}	Time to reach maximum concentration
TOI	Trial Outcomes Index
TSST	Time to second subsequent therapy (defined as time from randomization to the start of second subsequent therapy or death)
ULN	Upper limit of normal
USPI	United States Prescribing Information
VUS	Variants of unknown significance
wt	Wildtype

EXECUTIVE SUMMARY

The Oncologic Drugs Advisory Committee is convened to discuss new drug application (NDA) 206162 for olaparib 50 mg capsules. AstraZeneca is seeking accelerated approval for olaparib (400 mg twice daily [bd], until disease progression) in the following proposed indication:

Olaparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed (PSR) ovarian cancer (including fallopian tube or primary peritoneal) with germline BRCA (gBRCA) mutation as detected by an FDA-approved test, who are in response (complete response or partial response) to platinum-based chemotherapy.

Olaparib is a first in class polyadenosine 5'phosphoribose polymerase (PARP) -1,-2,-3 inhibitor, which selectively exploits deficiencies in DNA homologous recombination repair pathways in cancer cells. Treatment with olaparib leads to increased accumulation of DNA damage and cancer cell death. *BRCA1* and *BRCA2* gene mutations (*BRCAm*) are the most common function-altering mutations associated with homologous recombination deficiencies (HRD). Hereditary *BRCAm* carriers (ie, patients with *gBRCAm*) are commonly detected through blood testing, often performed according to NCCN guidelines ([NCCN 2012](#)) in all patients with serous ovarian cancers, regardless of age and family history.

No medicines are approved by the US Food and Drug Administration (FDA) as maintenance treatment for women with high-grade serous ovarian cancer who have initially responded to platinum-based chemotherapy, but whose disease has subsequently relapsed after completion of chemotherapy. The standard of care after completing 4 to 6 courses of chemotherapy is to watch and wait for several months until the next relapse manifests itself, usually leading to treatment with another line of cytotoxic chemotherapy. No treatments are approved specifically targeting the HRD pathway or the biological vulnerability associated with *gBRCAm*.

This briefing book outlines why AstraZeneca believes this NDA for olaparib meets the FDA's criteria for accelerated approval, based on the following:

- Relapsed high-grade serous ovarian cancer is a serious disease. Although chemotherapy is active in this setting, toxicity prevents its continuation to maintain the response achieved ("maintenance treatment"). In accordance with NCCN guidelines, the standard of care for patients who achieve response/disease stabilization after platinum-based chemotherapy is to "watch and wait" until progression. Patients receive multiple lines of chemotherapy, but the progression-free intervals become shorter with each subsequent line of therapy. The disease is incurable and patients will ultimately succumb to their disease. There is a clear need for improved treatment options in these patients. Such options could include maintenance treatment to substantially delay the time to subsequent progression, the need for subsequent lines of chemotherapy and extend the watch and wait time with minimally demanding treatment and good tolerability.

- This NDA is based primarily on the results of a well-conducted randomized placebo-controlled Phase II study (Study 19) in 265 patients with platinum-sensitive relapse (PSR) of high-grade serous ovarian cancer. The study specifically tested if maintenance therapy with olaparib 400 mg bd (after having completed platinum therapy prior to study entry) would substantially extend the time to progression compared with placebo. Platinum sensitivity, a study entry criterion, enriched for patients with DNA repair deficiencies.
 - Study 19 was a positive study. In the primary analysis in the intent to treat (ITT) population, a large and statistically significant improvement in progression-free survival (PFS) was demonstrated with olaparib as maintenance therapy after completion of platinum-based chemotherapy (HR=0.35, median 8.4 months vs 4.8 months for olaparib vs placebo, respectively; $p<0.00001$).
 - As planned by study design, and as predicted by the biology of PARP and the pharmacological properties of olaparib, AstraZeneca has further demonstrated that the subgroup of patients with a germline *BRCA* (*gBRCA*) mutation ($n=96$) derive greater benefit from olaparib treatment (HR=0.17; 11.2 months vs 4.1 months in the olaparib and placebo arms, respectively). This was confirmed by blinded independent review and robust sensitivity analyses. The magnitude of improvement in PFS along with an acceptable risk-benefit profile, as discussed below, is clinically meaningful and supportive of approval.
 - Findings in patients without *BRCA* mutations were positive, but less compelling, and not considered to be of sufficient degree to establish clinically meaningful benefit to these patients.
 - Overall survival (OS) analysis showed no evidence of benefit and there was no statistically significant difference (HR=0.85; median 32.9 months vs 30.2 months for olaparib vs placebo, respectively, in the *gBRCAm* subgroup).
 - An exploratory analysis requested by European Agencies and shared with FDA, the time from randomization to the second subsequent therapy or death (TSST), showed that the delay in first progression event (PFS) was carried forward. The median TSST in *gBRCAm* patients was 22 months vs 15 months (HR=0.43) for olaparib vs placebo, respectively. Based on this analysis, treatment with olaparib did not appear to affect sensitivity to subsequent chemotherapy. Of the 96 patients with *gBRCAm* randomized in the study, 57% and 86% received any subsequent line of therapy, for olaparib and placebo, respectively. Of note, 13/43 (30%) placebo patients (and none in olaparib group) in the *gBRCA* subgroup received an investigational PARP inhibitor as a subsequent therapy, all after completing Study 19.
- The NDA is supported by Study 41, an open-label randomized study ($n=162$ patients), which tested the role of olaparib in combination with carboplatin (both at reduced

doses, 200 mg bd and AUC4, respectively) and standard dose of paclitaxel 175 mg/m² for six 21-day cycles followed by full dose of maintenance olaparib (400 mg bd), vs standard doses of carboplatin (AUC6) and paclitaxel for six 21-day cycles followed by watch and wait with no further treatment.

- The overall study was positive on the primary endpoint of PFS in the ITT population (HR 0.51). Study 41 replicated the finding of Study 19 with greater treatment benefit in the population of patients (n=41) with a *BRCA* mutation (PFS HR=0.21; median not reached olaparib vs 9.7 months comparator arm; p=0.0015). There was no evidence of an OS benefit.
- To further support the NDA, the single agent activity of olaparib in *gBRCAm* patients with ovarian cancer has also been demonstrated in Study 12, a randomized dose finding study of olaparib (200 mg and 400 mg bd) vs pegylated liposomal doxorubicin (PLD) (n=97), as well as within a series of smaller non-controlled studies.
 - In Study 12, PFS was similar for olaparib compared with PLD (HR=0.88), an approved and recommended standard treatment for patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. Objective response rate was 25%, 31% and 18% for olaparib 200 mg bd, 400 mg and PLD, respectively.
 - Furthermore, consistent response rates (ie, complete response or partial response by RECIST) have been demonstrated across multiple supportive efficacy studies of olaparib in *gBRCAm* patients and in Study 19 (33%, 98/294 overall evaluable for response).
- The safety and tolerability profile of the 400 mg bd dose of olaparib (as determined in Study 19, and across the entire clinical development program) is appropriate for prolonged maintenance therapy as per the proposed indication. Although adverse events of nausea, vomiting, fatigue and anemia (generally low grade and intermittent) were reported commonly with olaparib, the majority of patients were able to stay on treatment for extended periods of time: at 3 years after randomization, 14% vs 2% in the ITT population, and 17% vs 5% in the *gBRCAm* subgroup remained on treatment for olaparib vs placebo, respectively.
- Germline *BRCA* mutations are commonly identified in patients by a widely available blood test, delivered by Myriad Genetics Laboratories Inc. in the US, which has been in use since 1994 as a laboratory developed test (LDT) for determination of hereditary breast and ovarian cancer risk. AstraZeneca is working with Myriad Genetics Laboratories Inc. to gain FDA approval for this test as a companion diagnostic for olaparib in the proposed *gBRCAm* indication. To date, Myriad has conducted more than 1 million tests and currently delivers approximately 150,000 *BRCA* tests per year.
- A randomized placebo-controlled confirmatory Phase III study (SOLO2) in 264 patients with platinum-sensitive relapse of recurrent ovarian cancer and a *BRCA*

mutation, is well underway and is expected to be fully accrued by Q1 2015. The required number of 158 PFS events will likely be observed by the end of 2015, with the analysis and regulatory review occurring approximately 2 years from now. SOLO2 is designed to confirm with great precision the magnitude of the PFS benefit, to likely equal or exceed 6 months in difference of medians, in prospectively accrued patients with PSR and *gBRCAm*. Overall survival is a secondary endpoint, and patient reported outcome and quality of life will be assessed.

Progression-free survival (PFS), when reliably assessed in the context of a placebo controlled double blind design, provides a meaningful evaluation of a treatment effect as it relates to tumor growth, tumor burden and disease progression. PFS is not affected by subsequent therapies. PFS may support registration in relapsed ovarian cancer provided it is of sufficient magnitude (that is clinically meaningful) and within the context of a positive risk-benefit profile ([Trabectedin ODAC transcript, 2009](#)). This is consistent with FDA feedback provided to AstraZeneca through a Type C regulatory interaction to discuss the design of the SOLO2 trial (2012). This is further supported by the clinical gynecological oncology community, including the Society of Gynecologic Oncology ([Herzog et al 2014](#)) and the Ovarian Cancer National Alliance ([OCNA 2011](#)). Analysis of PFS in Study 19 was robust, conducted in a blinded randomized setting, confirmed by blinded independent central review, and with sensitivity analyses demonstrating robustness, in particular with respect to possible evaluation time bias (eg, timing of assessment). Similar robust methodology is built into the Phase III SOLO2 design.

Consistent with Subpart H regulations, AstraZeneca is seeking accelerated approval for this NDA based on PFS, ie approval based on an effect on a clinical endpoint other than overall survival. The 7.1 month improvement in median PFS observed with olaparib, within the context of a favorable risk:benefit profile, represents a direct clinical benefit in support of approval (FDA Guidance; Clinical Trial Endpoints For The Approval of Cancer Drugs and Biologics 2007; [FDA 2007](#)). The confirmatory study (SOLO2) is designed to precisely confirm the magnitude of PFS benefit observed in *gBRCAm* patients in Study 19. The study is well underway and projected to be fully accrued by early 2015. Based on the pre-specified number of events (158 PFS events), the primary PFS analysis for SOLO II is anticipated to occur in late 2015, with regulatory submission of the results occurring by mid 2016.

Relapsed ovarian cancer is invariably a fatal disease

Ovarian cancer is generally detected at an advanced stage, with 5-year survival rates of 27% ([Siegel et al 2013](#)). Carboplatin- and cisplatin-based therapies are the main cytotoxic regimens for these patients ([Ledermann and Kristeleit 2010](#)). Although 70% to 80% of patients respond to such initial treatment, the majority subsequently relapse ([Ledermann and Kristeleit 2010](#)). Once relapsed, disease is no longer considered curable. Over the course of their disease, platinum-sensitive patients receive multiple lines of chemotherapy; for example >65% of patients went on to receive ≥ 4 lines of subsequent therapy after randomized study treatment in the OCEANS study with AVASTIN ([Bevacizumab EPAR 2012](#)). The benefit of continued platinum beyond 6-8 cycles in a recurrent setting is unclear, and is associated with increasing cumulative toxicities. Patients experience progressively shorter progression-free

intervals following later lines of therapy and ultimately succumb to their disease (Colombo et al 2010).

These chemotherapies are associated with high incidence of side effects such as nausea and vomiting (92%) and vomiting (81%), and patients require prophylactic anti-emetic treatment (Carboplatin USPI BMS 2008). Cisplatin, an alternative platinum agent, is additionally associated with cumulative renal toxicity (Platinol USPI 2010). Myelosuppression (neutropenia, thrombocytopenia and anemia) is generally the dose-limiting toxicity. Additional and/or exacerbated toxicity occurs with combination regimens. For example, in the comparator arm of the OCEANS trial, 82.4% of patients had grade ≥ 3 adverse events, including 21.9% with grade ≥ 4 neutropenia when treated with carboplatin in combination with gemcitabine (Aghajanian et al 2012).

Whilst physicians are adept at managing the toxicities of chemotherapy, these cumulative toxicities do limit the administration of platinum-based regimens. Treatment is therefore stopped prior to disease progression in most cases, and active surveillance continues, but without active maintenance therapy. From the patients' point of view, the watch and wait strategy is standard of care.

The unique biology of polyadenosine 5'diphosphoribose polymerase (PARP) and its connection to *BRCA* gene deficiency

Numerous DNA single stranded breaks (SSBs) occur naturally as the result of normal metabolic activities and environmental factors, including UV light and radiation. PARP plays an important role in identifying and repairing SSBs. Olaparib, through direct PARP enzyme inhibition and trapping of PARP with the DNA in an open configuration, prevents repair of SSBs. As cells undergo replication, SSBs are converted to harmful double-strand breaks (DSBs). In normal cells, DSBs are repaired by a DNA repair mechanism called homologous recombination repair. Cells with homologous recombination repair deficiency (HRD), resort to the more error prone repair mechanism called non-homologous end joining. In cells with HRD, DNA damage accumulates and leads to high genomic instability and eventual cell death. Cancer with HRD would thus be more sensitive to induction of cell death by PARP inhibitors.

To date, there is no well-established and available-for-testing single genetic/genomic signature which defines HRD. The most common function-altering mutations associated with HRD are a mutation in the breast cancer susceptibility gene (*BRCA*) *BRCA1* or *BRCA2* genes, which code for two of the critical proteins in homologous recombination repair. *BRCA1* and *BRCA2* mutations that are defined as deleterious and suspected deleterious mutations, are associated with loss of function of the protein. They are well validated through extensive study at Myriad Genetics Inc. (a commercial provider of germline *BRCA* gene testing), and in the clinical and research community.

Consistent with the DNA repair biology, individuals with hereditary *gBRCA* mutations have an increased risk of breast, ovarian, pancreatic and other cancers. The cancer cells in such individuals have lost the second normal copy of the *BRCA* gene (loss of the wildtype allele), whereas their normal cells still have one normal allele as well as one mutated allele. Normal cells in patients who carry a *gBRCA* mutation can therefore repair DSBs with the functioning

wildtype *BRCA* allele. In cancer cells, the loss of heterozygosity leaves the non-functional *gBRCA* allele as the sole copy. PARP inhibition takes advantage of this difference and preferentially kills the cancer cells with minimal toxicity to normal cells ([Rottenberg et al 2008](#); [Hay et al 2009](#)).

Deficiencies in other known homologous recombination repair pathway proteins (eg, ATM, RAD51, DSS1, RAD54, RPA1, NBS1, ATR, CHK1, CHK2, FANCD2, FANCA, and FANCC) may confer sensitivity to PARP inhibitors ([McCabe et al 2006](#)). However, these occur less commonly than *BRCA* mutations in ovarian cancer ([Pennington et al 2014](#)) and currently there is no simple assay to define an 'HRD phenotype'.

HRD increases sensitivity to platinum-based chemotherapy, as the deficiency impairs the ability of cancer cells to repair the direct platinum-induced double strand DNA breaks. Thus, platinum sensitivity is often associated with an HRD tumor type. This approach to enriching for the HRD phenotype was used in the pivotal study for this NDA.

Clinical pharmacology

Olaparib is a potent, selective PARP-1, -2 and -3 inhibitor. It has a T_{max} of 1-3 hours and mean terminal half-life of approximately 12 hours. It is metabolized primarily by the CYP3A4 enzyme and is excreted through the urine (35% to 50%) and feces (12% to 60%). The capsule formulation in this NDA is the proposed commercial formulation. The maximum tolerated capsule dose of 400 mg bd has better clinical efficacy in terms of objective response and PFS when compared with 200 mg bd, while the 100 mg bd dose is only minimally effective.

Key efficacy findings: pivotal Study 19

Study 19 is a double-blind, randomized, placebo-controlled phase II study in 265 patients with platinum sensitive relapsed (PSR) high-grade serous ovarian cancer (please see [Figure 3](#) for study schema overview). Patients were randomized 1:1 to either olaparib 400 mg bd or placebo maintenance treatment following chemotherapy ([Ledermann et al 2012](#)). Based on the known biology of PARP, the accrued population was expected to be enriched for the HRD phenotype, including but not limited to *BRCA* mutation. Study 19 was originally designed with two co-primary analyses: the first comprising all patients (itself a selected, HRD-enriched population, based on platinum sensitivity), and the second comprising a HRD subset based on a to-be-defined specific assay. Prior to any analysis, the HRD co-primary analysis was removed because a general HRD test had not become available. A *BRCA* subgroup analysis based on prospectively collected *BRCA* mutation status by local testing was a pre specified secondary sub-group analysis in the statistical analysis plan (SAP).

Study 19 met its primary endpoint and demonstrated a statistically significant improvement in PFS in the overall patient population (data cut-off [DCO] 30 June 2010):

- A 65% reduction in the risk of death or disease progression (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.25-0.49; $p < 0.00001$; median PFS 8.4 months vs 4.8 months in the olaparib and placebo arms, respectively).

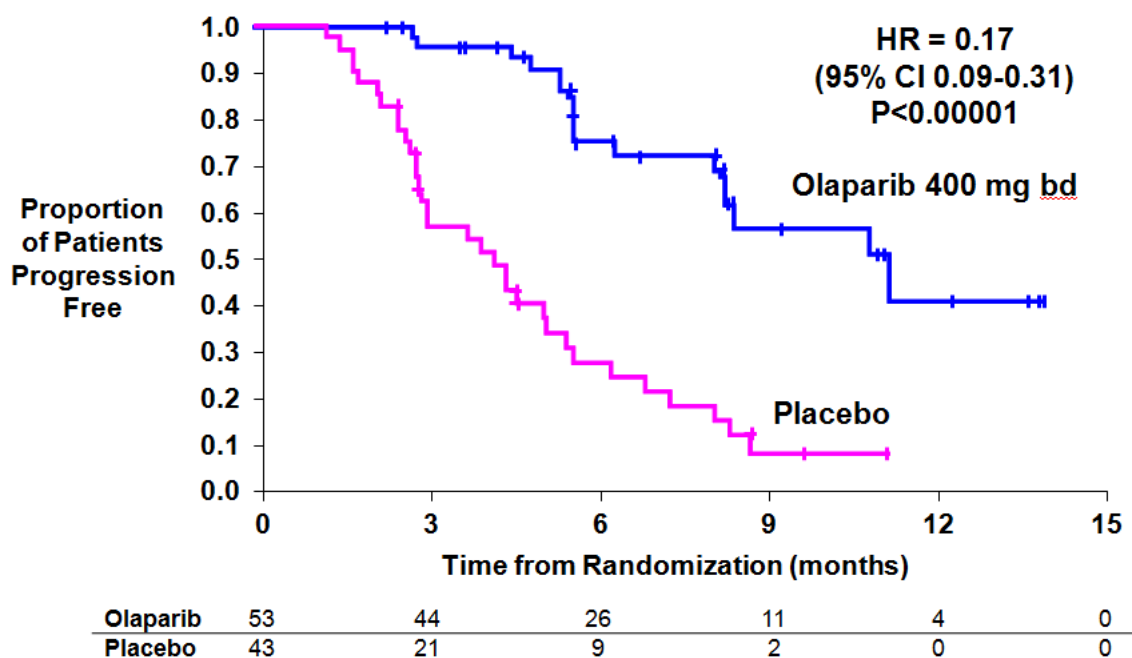
- As predicted by the DNA repair biology and the pharmacology of olaparib, the small number (n=59) of patients known prospectively to have a *gBRCA* mutation based on local testing (ie, recorded on CRFs at study entry), experienced statistically significant greater improvement in PFS over placebo in this subgroup (PFS HR 0.11; 95% CI 0.04-0.27; $p<0.00001$).
- To provide a more comprehensive dataset for *BRCAm* patients, *BRCA* mutation status was determined subsequently by centrally testing blood and archival tumor samples, which were collected prior to randomization from all patients with appropriate consent for optional genetic testing. Mutation status assessments were conducted blinded to treatment and other clinical outcome data, including *gBRCA* mutation status recorded on the case report form (CRF) at study entry. When all sources of information were combined (CRF data, plus blood and tumor testing) *BRCA* mutation status was determined for 96% (254/265) of patients, including 96 patients with *gBRCA* mutation (53 in the olaparib arm and 43 in the placebo arm).

The PFS analysis was re-run by updated *BRCA* mutation status (using DCO 30 June 2010) and an updated and more mature planned survival analysis was conducted for the overall population and by *BRCA* subgroup (DCO 26 November 2012). Results were highly consistent whether *BRCA* mutation status was based on combined blood or tumor, or blood testing alone.

For the purpose of this briefing book, as the companion diagnostic will be a blood-based test for determination of germline *BRCA* mutation status (the Myriad Integrated BRACAnalysis[®] test), efficacy presentations will focus on the 96 patients who had *gBRCA* mutations. Key results from the updated analysis of Study 19 data are summarized below and in [Table 1](#):

- Consistent with the biological rationale, subgroup analyses consistently demonstrate that greater clinical benefit is observed across the *gBRCAm* subgroup. The benefit was less pronounced in the overall population and in patients without *gBRCA* mutation, although some benefit was seen.
 - In Study 19, the subgroup of patients with a germline *BRCA* (*gBRCA*) mutation (n=96; the population serving as primary evidence for the proposed labelling) showed ([Figure 1](#)) greater benefit from olaparib treatment (HR=0.17; 11.2 months vs 4.1 months in the olaparib and placebo arms, respectively, $p<0.00001$). This was confirmed by blinded independent review and robust sensitivity analyses.
 - Findings in the ‘non *gBRCA*’ subgroup (ie, wildtype/variant of unknown significance [VUS]) are also positive, albeit with smaller risk reduction (PFS HR 0.50; 95% CI 0.29–0.82; $p=0.00572$), with a 2.8 month extension in median PFS over placebo. This positive finding is consistent with enrichment for the HRD phenotype across the entire ITT population, including HRD due to mechanisms other than *gBRCA* mutation. However, it appears quantitatively different from *gBRCAm* and not of sufficient magnitude to be considered a clinically meaningful benefit.

Figure 1 PFS in patients with *gBRCA* mutation– Study 19



- The PFS analysis is robust: all sensitivity analyses (evaluation–time bias analysis, attrition bias, stratified log rank test, cox model including *BRCA* mutation status) and the blinded independent central review (BICR) of scan assessments (PFS HR 0.25; 95% CI 0.13-0.49; p=0.00003 in the *gBRCA* subgroup) confirm this risk reduction in disease progression or death (see Section 9 in appendices for more information).
- Furthermore, the risk reduction in disease progression or death was similar regardless of whether *gBRCA* mutation status was determined prospectively (CRF entries based on local test) or retrospectively (updated analysis).

There was no statistically significant difference in overall survival (OS) in the overall population (HR 0.88; 95% CI 0.64–1.21; p=0.44; 58% maturity) or in the *gBRCAm* subgroup (HR 0.85, 95% CI 0.48-1.52, p=0.58, median OS 32.9 months vs 30.2 months in favor of olaparib vs placebo; 52% maturity). However, although no cross-over was permitted as part of the study, a considerable proportion of patients in the placebo arm of Study 19 received an investigational PARP inhibitor post-study (13/43; 30% of patients in the *gBRCA* subgroup).

In response to guidance from European authorities, exploratory analysis of time from randomization to second subsequent therapy or death (TSST) was undertaken. In this analysis, randomization was preserved by including all patients who received randomized study treatment (includes 264/265 patients in Study 19, as one patient [in the placebo arm] did not receive randomized treatment); patients who did not have second progression were censored at the time they were last known to be alive. In the *gBRCAm* subgroup, olaparib

extended TSST by 7 months compared with placebo (HR 0.43; 95% CI 0.25–0.71; $p=0.00099$; 22 months vs 15 months), providing reassurance that sensitivity to subsequent chemotherapy was not impaired by olaparib. In the *gBRCA* subgroup, 57% vs 86% of patients received subsequent therapy in the olaparib vs placebo arms, respectively (median numbers of subsequent lines of therapy were 1 vs 2, respectively).

Olaparib maintenance therapy demonstrated no detrimental impact on health-related quality of life (HRQoL) outcomes compared with placebo.

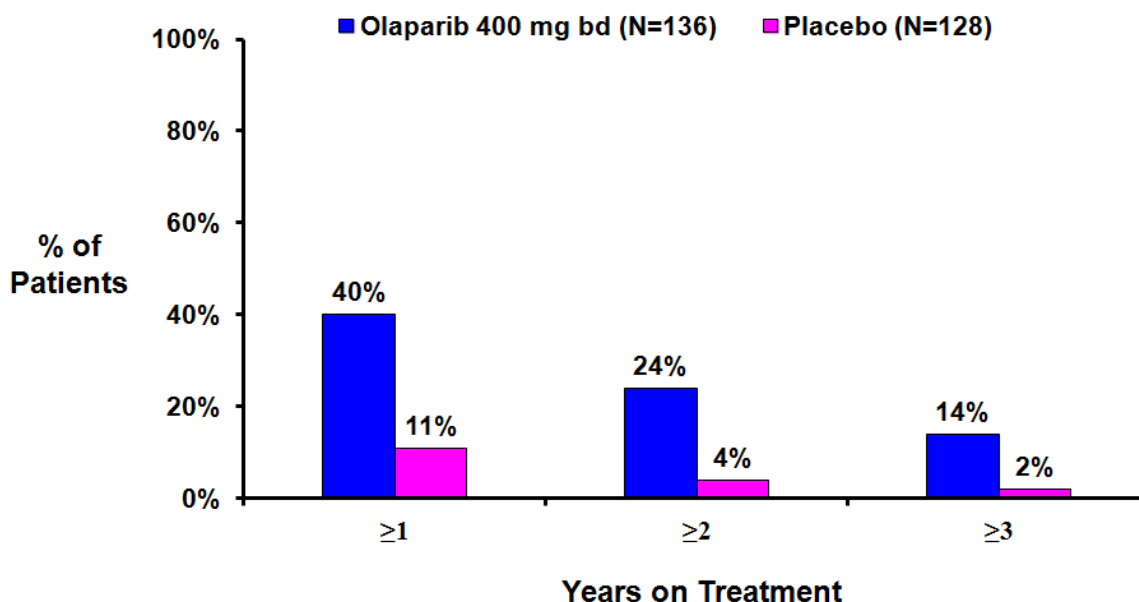
Key clinical safety results

Based on the entire clinical development program (2618 patients exposed to olaparib up to 02 May 2014) olaparib has an acceptable safety and tolerability profile suitable for prolonged administration as maintenance monotherapy in patients with relapsed ovarian cancer. The 400 mg bd dose was well tolerated and – even taking into account dose interruptions and reductions, which were permitted to manage adverse events (AEs) – the majority of patients in Study 19 received 600 mg to 800 mg daily throughout the treatment period, with infrequent discontinuation due to adverse events.

In Study 19 ($n=264$ in the safety analysis population; 136 vs 128 in the olaparib and placebo group, respectively), the 400 mg bd dose was generally well tolerated, regardless of *BRCA* mutation status.

As shown in Figure 2 for the safety population, a considerably greater proportion of patients in the olaparib arm stayed on assigned treatment for 1, 2 and 3 years, compared with the placebo arms. The same was true in the *gBRCA* subgroup: 45% vs 9% at 1 year, 25% vs 7% at 2 years, and 17% vs 5% at 3 years in the olaparib and placebo arms, respectively.

Figure 2 Duration of study treatment in Study 19: Safety Analysis ($n=264$)



The most common AEs in olaparib-treated patients were nausea (71%), fatigue (52%), vomiting (34%) and anemia (21%). These events were generally intermittent and of a low grade (grade 1 or 2).

A higher proportion of patients in the olaparib arm had serious adverse events (SAEs) compared with placebo (18.4% vs 8.6%). The reporting rates for individual SAEs were low with no single MedDRA preferred term reported in more than 1 patient in the *gBRCAm* subgroup.

The safety findings in the *gBRCAm* subgroup were consistent with the safety findings in the overall population in Study 19, and consistent with the safety assessment across the 735 patients who received olaparib 400 mg bd capsules as monotherapy in the clinical trial program.

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) are events of special interest that could potentially be related to products that affect DNA repair mechanisms. These risks were evaluated from SAE reports across the entire olaparib dataset (N=2618). As of 02 May 2014, MDS/AML was reported in 0.8% (21/2618) of patients treated with olaparib and 1.3% (2/160) patients on placebo (n=1) or comparator (pegylated liposomal doxorubicin) (n=1).

Chemotherapy and radiotherapy are risk factors for secondary MDS/AML and these incidences are consistent with literature reports for patients who have received chemotherapy/radiation therapy for ovarian cancer. This potential risk will be further characterized in an additional 2683 patients (planned enrolment) with *BRCA* mutation (predominantly *gBRCAm*) in the ongoing phase III program, including continued active monitoring and investigation of AEs of special interest, with prompted follow-up for reports.

SOLO2: confirmatory phase III study

A randomized controlled Phase III trial (SOLO2) is well underway in patients with *BRCA* mutation. Consistent with accelerated approval guidelines (Subpart H), SOLO2 is designed to provide confirmatory evidence of the magnitude of PFS benefit observed in *gBRCAm* patients in Study 19. SOLO2 is expected to be fully enrolled with 264 patients in 1Q2015. The primary analysis will be triggered when approximately 158 PFS events have occurred (expected end of 2015), with submission of results and regulatory review anticipated by mid 2016.

Regulatory feedback regarding the design of the SOLO2 study was sought from FDA through a Type C interaction in October 2012. The Agency advised that “A clinically meaningful improvement of PFS (ie, equal to or greater than the six-month improvement in PFS seen in *gBRCA* mutation positive patients in Study 19) along with an acceptable risk-benefit profile may be an acceptable endpoint to support approval in the relapsed setting; however, you should note that a statistically significant difference in PFS may not demonstrate a clinically meaningful difference. Whether PFS is appropriate for forming approval of olaparib in the

relapsed setting will be a review issue. If you [AstraZeneca] do not believe that you will demonstrate results similar to Study 19, we [FDA] recommend that OS be a primary or co-primary endpoint.”

AstraZeneca believes that SOLO2 will demonstrate similar results to Study 19. Accordingly, PFS is the primary endpoint in SOLO2, and the study is sized based on this primary endpoint. Overall survival will be characterized as a secondary endpoint. This approach is consistent with the recent Society of Gynecologic Oncology White Paper ([Herzog et al 2014](#)), which concludes that a large magnitude of effect in PFS improvement is clinically meaningful for ovarian patients and the feasibility of demonstrating an effect on OS in ovarian cancer is compromised by a prolonged time-line for final analysis, and the potential for unintended loss of treatment effect from multiple lines of active post-progression therapies.

Olaparib has a favorable benefit-risk profile as maintenance treatment for patients with platinum-sensitive relapse (PSR) of high-grade serous ovarian cancer and a *gBRCA* mutation

- Olaparib is a unique oral therapy that offers clinically meaningful benefit with an unprecedented magnitude of improvement in PFS. The safety profile of olaparib is appropriate for long term administration as maintenance monotherapy and an unusually high proportion of patients have been able to stay on olaparib for in excess of 3 years.
- Olaparib is the first therapy targeted to *BRCAm* disease in patients with PSR ovarian cancer and a germline *BRCA* (*gBRCA*) mutation. Study 19 demonstrated a clinically meaningful and highly statistically significant benefit in PFS in patients with a *gBRCA* mutation.
- Olaparib demonstrates a positive benefit risk profile for sustained use as oral maintenance therapy until documented disease progression. It fulfills a high unmet medical need in this incurable disease setting where patients relapse and receive multiple lines of chemotherapy with their associated toxicity and morbidity, which are interrupted by periods of watch and wait due to the cumulative toxicity of platinum-based regimens.
- AstraZeneca considers that the findings from Study 19 meet the regulatory criteria for accelerated approval ([FDA 2013](#)). It is anticipated that the clinical benefit demonstrated in the subgroup analyses in *gBRCAm* patients will be confirmed in the ongoing Phase III study (SOLO2) in *BRCAm* patients. Recruitment into SOLO2 is well underway and is part of a comprehensive drug development plan for olaparib.
- AstraZeneca commits to work with the Agency to review results from across the development program, including SOLO2, and if these are not confirmatory in nature, will consequently abide by the results and take the necessary actions, which could include withdrawal of the NDA.

Table 1 Summary of key efficacy outcomes from Study 19 (pivotal phase II PSR ovarian maintenance study)

	Intent to treat ^a (N=265)		<i>gBRCAm</i> (determined by blood testing) (N=96)	
	Olaparib (n=136)	Placebo (n=129)	Olaparib (n=53)	Placebo (n=43)
Progression-free survival (PFS) – DCO 30 June 2010				
No events: No patients (%)	60:136 (44%)	94:129 (73%)	17:53 (32%)	33:43 (77%)
Median time months)	8.4	4.8	11.2	4.1
HR (95% CI)	0.35 (0.25–0.49)		0.17 (0.09-0.31)	
P value (2-sided)	p<0.00001		p<0.00001	
Time from randomization to second subsequent therapy or death (TSST) – DCO 26 November 2012				
No events: No patients (%)	88:136 (65%)	108:128 (84%)	29:53 (55%)	34:43 (79%)
Median time (months)	19.1	14.8	22.0	15.0
HR (95% CI)	0.53 (0.40–0.71)		0.43 (0.25-0.71)	
P value (2-sided)	p=0.00001		p=0.00099	
Overall Survival (58% maturity in ITT population, 52% in <i>BRCAm</i> population) – DCO 26 November 2012				
No events: No patients (%)	77:136 (57%)	77:129 (60%)	27:53 (51%)	22:43 (51%)
Median time (months)	29.8	27.8	32.9	30.2
HR (95% CI)	0.88 (0.64–1.21)		0.85 (0.48-1.52)	
P value (2-sided)	p=0.44		p=0.58	

CI = confidence interval; DCO = data cut-off; HR = hazard ratio

a TSST in Study 19 was analyzed in the Safety Analysis (n=264), excluding the single patient [in the placebo arm] who did not receive randomized treatment.

1. BACKGROUND

Olaparib is a first in class novel oral PARP inhibitor that exploits deficiencies in DNA repair pathways to preferentially kill cancer cells. On 03 February 2014 AstraZeneca submitted a New Drug Application (NDA) in support of the following proposed indication and dose:

- Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed ovarian cancer (including fallopian tube or primary peritoneal) with germline *BRCA* (*gBRCA*) mutation as detected by an FDA-approved test, who are in response (complete response or partial response) to platinum-based chemotherapy.

- The recommended dose of olaparib capsules is 400 mg (eight 50 mg capsules) taken twice daily (bd), equivalent to a total daily dose of 800 mg.

1.1 Platinum-sensitive relapsed ovarian cancer

1.1.1 Ovarian cancer

Ovarian cancer is a serious and life-threatening disease and an important public health issue, ranking as the fifth most common cause of cancer death in women in the US. In 2013, there were an estimated 14,030 deaths due to ovarian cancer and 22,240 new cases of ovarian cancer ([American Cancer Society 2013](#)).

Early diagnosis of ovarian cancer remains a challenge with 75% of patients presenting with advanced disease (Stage III or IV). Almost all patients have tumor recurrence despite aggressive treatment ([Hennessy et al 2009](#)). First-line platinum containing chemotherapy, gives response rates up to 80% and is the current standard of care. The majority of patients subsequently die of recurrent disease, with 5-year survival rates of 44% across all stages and 27% for advanced stages ([Siegel et al 2013](#)). The majority of deaths are from ovarian cancer of the high grade serous histological type ([Colombo et al 2010](#)). Three subgroups of patients with relapsed ovarian cancer have been identified:

- Platinum-refractory disease that progresses during platinum treatment
- Platinum-resistant disease that develops recurrence <6 months from the completion of platinum chemotherapy
- Platinum-sensitive disease, defined by a relapse-free period of ≥ 6 months following the last dose of prior platinum treatment ([Colombo et al 2010](#)).

1.1.2 Platinum-sensitive relapsed ovarian cancer

Despite initial responses to platinum-based therapies, relapsed disease is considered to be incurable and patients ultimately die from their disease ([Colombo et al 2010](#)).

Patients with platinum-sensitive relapses are generally retreated with platinum-containing chemotherapies until such time as the disease becomes platinum-resistant or the patient develops treatment hypersensitivity or unacceptable toxicity. It is therefore common for these patients to receive multiple lines of chemotherapy, which likely confounds overall survival analysis. For example, in the OCEANS bevacizumab trial in the second-line treatment setting, >65% of patients went on to receive ≥ 4 lines of subsequent therapy after randomized study treatment (Table 19 of the [Bevacizumab EPAR 2012](#)). Median overall survival in this trial was 35.2 months in patients treated with gemcitabine and carboplatin ([Aghajanian et al 2012](#)). Although high response rates of 84% to 91% can be achieved following retreatment at first relapse ([Rose et al 1998](#); [Gronlund et al 2001](#)), the time to progression generally shortens with consecutive therapies. The goals of treatment for relapsed disease shift to providing disease control and symptom palliation whilst minimizing the toxicity burden for patients during each line of treatment.

A number of combination chemotherapy regimens are established in PSR ovarian cancer, most commonly combining carboplatin with another chemotherapy agent. Toxicities limit the number of cycles of chemotherapy that can be given at each relapse, as chemotherapy not only damages and kills tumor cells but also normal cells. Chemotherapy therefore cannot be continued indefinitely. Post-chemotherapy, as standard of care patients are monitored and undergo regular screening for disease progression.

Platinum-based chemotherapy regimens are associated with clinically impactful toxicities. Myelosuppression, whilst manageable by treating physicians, is generally the dose-limiting toxicity limiting the number of cycles that can be given at each line of therapy. Nausea and vomiting occur frequently and require prophylactic antiemetic administration ([Carboplatin USPI BMS 2008](#)). Additionally, carboplatin hypersensitivity reactions develop in a significant proportion of patients with retreatment (up to approximately 25% in patients receiving more than seven cycles of carboplatin; [Castells et al 2008](#)), causing symptoms that range from cutaneous reactions and gastrointestinal upset to life-threatening respiratory and cardiovascular compromise. Other toxicities more common with cisplatin include peripheral neurotoxicity and ototoxicity, which may be irreversible and result in considerable negative impact on quality of life, as patients may experience severe neuropathic pain, paraesthesia and hearing impairment ([McWhinney et al 2009](#)). Cisplatin is also associated with cumulative renal toxicity ([Platinol USPI 2010](#)). Additional and/or exacerbated toxicity occurs with combination regimens ([Aghajanian et al 2012](#)). Whilst physicians are adept at managing the toxicities of such chemotherapy regimens, including hematological toxicity and hypersensitivity reactions, each administration impacts on the patient's normal life and requires a clinic visit, an intravenous line, pre- and post-treatment blood tests, and administration of prophylactic concomitant medications. Although retreatment with chemotherapy will ultimately be required in the relapsed disease setting, delaying this requirement with the associated toxicity and morbidity is considered desirable for and by patients.

FDA-approved treatments for ovarian cancer are limited to cytotoxic chemotherapy agents, including platinum agents (carboplatin, cisplatin), camptothecin/topoisomerase inhibitors (topotecan hydrochloride), anthracyclines (doxorubicin hydrochloride, pegylated liposomal doxorubicin hydrochloride), alkylating agents (cyclophosphamide), antimetabolite agents (gemcitabine hydrochloride) and antimicrotubule agents (paclitaxel). There are no treatments approved for use in the maintenance treatment setting.

Physicians treating ovarian cancer may additionally prescribe non-approved agents in line with national treatment practice guidelines, dependent on a patient's individual circumstances and treatment needs (eg, bevacizumab in line with NCCN treatment guidelines; [NCCN 2013](#)).

Because of the toxicity associated with approved and *de facto* used treatment for relapses of ovarian cancer, there is currently no opportunity to provide additional disease control and symptom palliation whilst minimizing the toxicity burden for patients in-between each line of treatment.

1.1.3 *BRCA* mutated (*BRCAm*) ovarian cancer

The *BRCA1* and *BRCA2* genes were identified in the early 1990's as genetic elements underlying inherited breast and ovarian cancer. *BRCA* mutations are particularly prevalent in persons of Jewish descent (Roa et al 1996) and often associated with high-grade serous ovarian cancer, where the germline *BRCA1* and *BRCA2* (*gBRCA*) frequency in unselected patients is as high as 17% (Alsop et al 2012a; Alsop et al 2012b) and up to 38% in patients with platinum-sensitive recurrent high-grade serous ovarian cancer (Dann et al 2012). Women inheriting a mutated copy of *BRCA1* or *BRCA2* have a 39% and 11% risk, respectively, of developing ovarian cancer by the age of 70 (Antoniou et al 2003).

Germline *BRCA1* mutation confers a higher risk of developing ovarian cancer than germline *BRCA2* mutation (Antoniou et al 2003) and ovarian tumors in *BRCA1* mutation carriers generally arise several years, and in some cases up to a decade, earlier compared with those in *BRCA2* (Alsop et al 2012a). Thus, *BRCA1* mutations are more commonly identified in ovarian cancer patients than *BRCA2* mutations, with mutation frequencies of 62% vs 38%, respectively (Alsop et al 2012a; Alsop et al 2012b).

In individuals inheriting a germline *BRCA* (*gBRCA*) mutation, only one allele carries the mutation in normal cells. As part of tumor genesis, cancer cells acquire additional somatic mutation or functional alteration or loss of the normal allele (loss of heterozygosity). In *BRCA1/2m* tumors, the loss of functional *BRCA1* or *BRCA2* protein results in a non-functioning homologous repair pathway (homologous recombination deficient [HRD]) requiring the use of alternative error-prone DNA repair pathways such as non-homologous end joining (McCabe et al 2006). Homologous recombination deficiency makes these tumor cells especially sensitive to double stranded DNA damaging agents, such as platinum (Lafarge et al 2001, Quinn et al 2003, Hennessy et al 2010).

BRCAm ovarian cancers can also arise as the result of sporadic somatic mutation in the tumor. Approximately 6% to 7% of high-grade serous ovarian cancers are estimated to harbor somatic tumor only mutations in *BRCA1/2* (Yang et al 2011; Hennessy et al 2010). Irrespective of whether the mutation is germline or somatic in origin, the functional relevance appears the same. The biology would not predict any difference in sensitivity to PARP inhibitors relative to the origin of the *BRCA* mutation. Similarly, a difference in PARP sensitivity would not be anticipated in patients with *BRCA1* compared with *BRCA2* mutations.

Mutations in the *BRCA* gene (point mutations/large rearrangements) are the major contributor to the loss of *BRCA1* and/or *BRCA2* protein function and mutation testing will detect the vast majority of these aberrations (named deleterious and suspected deleterious). Other loss of function mechanisms exist, such as epigenetic factors and aberrant expression of *BRCA1* or *BRCA2* through loss of heterozygosity or, in the case of *BRCA1*, through promoter hypermethylation. Deficiencies in other known homologous recombination pathway proteins are also recognized (including ATM, RAD51, DSS1, RAD54, RPA1, NBS1, ATR, CHK1, CHK2, FANCD2, FANCA, and FANCC) and are likely to confer sensitivity to PARP inhibition (McCabe et al 2006).

Consistent with this biology, patients with *BRCA* mutations often have platinum-sensitive epithelial ovarian cancer (Dann et al 2012; Hennessey et al 2010), associated with improved PFS outcomes (Tan et al 2008, Hennessey et al 2010). The largest series to date of 1,213 patients with *BRCA* mutations (Bolton et al 2012) decisively establishes that *BRCA1*- and *BRCA2*-associated ovarian cancers have a better prognosis compared with sporadic ovarian cancers (Hyman et al 2012). However, the overall pattern of disease remains similar, with disease recurrence after each line of chemotherapy and patients ultimately dying from their disease.

A recently published study explored the therapeutic impact of somatic *BRCA1/2* mutations and mutations in other homologous recombination DNA repair genes in 390 ovarian carcinomas from 367 patients (Pennington et al 2014). The gene panel included *BRCA1*, *BRCA2*, and 11 other genes in the homologous recombination pathway. In this analysis, 31% of patients with ovarian carcinomas had a deleterious germline (24%) and/or somatic (9%) mutation in one or more of 13 homologous recombination genes. The majority (74%) of these mutations occurred in *BRCA1* or 2 and the remaining 26% were spread across 11 HR genes: ATM, BARD1, BRIP1, CHEK1, CHEK2, FAM175A, MRE11A, NBN, PALB2, RAD51C, and RAD51D. As predicted by the biology, the somatic *BRCA1/2* mutations and mutations in other homologous recombination genes were reported to have a similar positive impact on overall survival and platinum responsiveness as germline *BRCA1/2* mutations.

1.1.4 Maintenance treatment for patients with platinum-sensitive relapsed *BRCA* mutated (*BRCAm*) ovarian cancer

Given that platinum sensitive ovarian cancer invariably recurs, instead of a ‘watch and wait’ strategy as in the current standard of care, an active maintenance therapy that can prolong PFS and delay the next line of chemotherapy by a clinically meaningful duration of time, would offer patients significant clinical benefit. By controlling disease after completion of chemotherapy and further delaying disease progression, an effective maintenance treatment approach would maintain patients in a well state for as long as possible, and reduce the physical and psychological anxiety experienced by patients whilst waiting for relapse of their disease after completion of chemotherapy. Maintenance therapy must of course be tolerable, with an acceptable long-term safety profile.

1.2 Mechanism of action of olaparib

Olaparib selectively exploits deficiencies in DNA homologous recombination repair pathways in cancer cells, leading to increased accumulation of DNA damage, which leads to cancer cell death.

Endogenous base damage is the most common form of DNA damage in cells. The base excision repair pathway recognizes damaged bases and, after excising them, generates DNA single strand breaks (SSBs). It is estimated that up to 20,000 SSBs occur every day in a metabolically active cell, with an even higher frequency in tumor cells. PARP-1 and -2 are associated with the repair of DNA SSBs, and while PARP-1 is the main family member

involved in the repair of DNA SSBs, PARP-2 still has the ability to compensate for PARP-1 activity ([Lindahl and Barnes 2000](#)).

In contrast, PARP-3 does not have a known role in the repair of DNA SSBs and, unlike PARP-1 and PARP-2 that have zinc-finger DNA binding domains, PARP-3 is not known to bind DNA directly. Instead, PARP-3 has been shown to interact with the chromatin binding factor aprataxin and PNKP like factor (APLF), which accelerates but is not essential for non-homologous end joining DNA DSB repair ([Rulten et al 2011](#)). Recent data suggest that PARP-3 inhibition does not contribute towards anti-tumor activity against *BRCAm* cancers ([Jaspers et al, 2013](#)).

In addition to enzymatic inhibition (IC_{50} of 5 nM, 1 nM and 4 nM, for PARP-1, -2 and -3, respectively), olaparib also involves the trapping of inactivated PARP onto SSBs, preventing their repair and generating a potential block for cellular DNA replication ([Helleday 2011](#); [Murai et al 2012](#)). Processing of trapped PARP-DNA complexes and/or the stalling and subsequent collapse of replication forks leads to deleterious DNA double strand breaks (DSBs). In replicating cells, DSBs would normally be repaired by the homologous recombination repair pathway, which requires functional BRCA1 and BRCA2 proteins. However, in the absence of functional BRCA1 or BRCA2 (such as in *BRCAm* tumors), repair must instead occur via alternative pathways such as the non-homologous end joining pathway, which are highly error prone and result in a significant increase in genomic instability. *In vivo*, BRCA1 and BRCA2 defective tumors are intrinsically sensitive to PARP inhibitors ([Rottenberg et al 2008](#); [Hay et al 2009](#)). Tumor cells carry a higher DNA damage load than normal cells ([Jackson and Bartek 2009](#)), and in an HRD tumor cell the accumulation of DNA damage will ultimately become insupportable ([Annunziata and Bates 2010](#)).

In individuals inheriting mutations in either of the *BRCA* genes, all normal (non-tumor) cells carry a second normal copy of the gene that can make functional BRCA protein. Thus such normal cells appear to have normal cellular function, although the implications of having only one functioning copy of the gene are not fully elucidated. *BRCA1* or *BRCA2* mutation carriers are at increased risk of a cell becoming cancerous due to loss of function of the remaining 'good-copy' of the gene(s), which leads to the loss of all functional BRCA protein(s), a scenario which would lead to increased DNA mutation and genomic instability ([Venkitaraman 2002](#)). This lack of functional BRCA1 or BRCA2 in tumors presents an opportunity for targeted treatment with PARP inhibitors because normal (non-tumor) cells have one functional copy of the *BRCA* gene and can produce normal, functional BRCA proteins. It is this fundamental difference in repair capability between tumors and normal cells that provides a favorable therapeutic window for olaparib single agent maintenance therapy.

2. CLINICAL PHARMACOLOGY OF OLAPARIB

Olaparib capsules are an oral formulation, containing 50 mg of olaparib. The capsules consist of olaparib drug substance suspended in the semi-solid excipient lauroyl macrogol-32 glycerides (LMG) within a white, opaque, hypromellose capsule shell.

The same olaparib capsule formulation has been used in all Phase I and II studies included in the NDA and is the proposed commercial formulation. In addition, an oral tablet formulation containing 100 mg or 150 mg of olaparib has been developed and is used within the Phase III program.

In both rat and dog, the principal target organ for toxicity following repeat dosing of olaparib for up to 1 or 6 months was the bone marrow: reductions in red and white blood cells, neutrophil and/or lymphocyte counts, and increases and/or decreases in reticulocyte and platelet counts. These changes were associated with increases in the erythropoietic and/or myelopoietic cell populations within the bone marrow, and with increases in splenic hemopoiesis, hepatocyte pigmentation and/or thymic atrophy. All changes seen in rats and dogs in the 1 month studies showed full or partial recovery following a 28 day recovery period.

Studies in rats and dogs showed no evidence of cardiac toxicity following oral dosing of olaparib. In a hERG channel assay, olaparib had an IC_{50} >110-fold higher than the human mean free C_{max} at the 400 mg bd clinical dose. In addition, in anesthetized dogs, olaparib showed no evidence for QT prolongation following intravenous administration. This suggests little potential for QT prolongation in humans at the proposed clinical dose.

The pharmacokinetics (PK) of olaparib capsule have been characterized in patients with advanced solid tumors, including ovarian or breast cancer with a *gBRCA* mutation. The pharmacodynamics (PD) have been characterized in patients with advanced solid tumors and patients with intermediate to high risk breast cancer scheduled for elective surgery. Key findings are:

- Following single oral dosing to cancer patients using the capsule formulation, olaparib was rapidly absorbed (t_{max} typically 1–3 hours). At a dose of 400 mg, mean apparent volume of distribution was 167 L, mean apparent clearance was 8.64 L/h and mean terminal half-life was 11.9 hours.
- On multiple dosing, there was no evidence of time dependency in the PK, or marked accumulation. Steady state olaparib exposure is expected to be achieved within 3 days of starting dosing.
- Exposure showed high inter-patient variability at all dose levels, increasing proportionally with dose at doses up to 100 mg twice daily (bd), but less than dose proportionally thereafter. Following dosing at 400 mg bd, the population model estimated steady state maximum plasma concentration ($C_{max ss}$) for individual patients ranged from 1.18 to 14.2 $\mu\text{g/mL}$ and the steady state area under the plasma concentration-time curve (AUC_{0-12}) ranged from 6.48 to 154 $\mu\text{g.h/mL}$.
- Recent results from an ongoing food effect study show that administration of olaparib in the fed state slows the rate of absorption and increases (by ~20%) the extent of absorption. Administration with food did not appear to change the high inter-patient

variability seen in exposure. It is recommended that patients should take olaparib at least one hour after food and refrain from eating for 2 hours afterwards.

- In radio-labeled studies of olaparib, unchanged drug accounted for approximately 70% of the circulating material in the plasma, the remainder accounted for by 3 other components (~10% each). Drug-related material was eliminated in urine and feces, predominantly as metabolites. Metabolism was extensive and predominantly a consequence of oxidation. The pharmacological activity of the 3 circulating metabolites is unknown.
- Clinical studies to date have included very few patients with moderate or severe organ impairment. Renal and hepatic impairment studies (dosed with the tablet formulation) are currently ongoing. Until further data are generated, it is not recommended that olaparib is dosed to patients with moderately or severely impaired renal function, or to patients with impaired hepatic function (serum bilirubin >1.5x upper limit of normal [ULN]).
- Patient age, race, gender or body weight were not found to be predictors of olaparib plasma exposure and therefore dose adjustment on the basis of individual patient demographics should not be required.
- In vitro data indicate that olaparib is unlikely to be associated with drug-drug interactions through inhibition or induction of CYP450 enzymes.
- In vitro, the metabolism of olaparib is predominantly via CYP3A. Clinical studies (olaparib tablet formulation) to evaluate the impact of a co-administered inhibitor or inducer of CYP3A are ongoing. Interim data show that average olaparib C_{max} and AUC are increased by 1.5- and 3-fold, respectively if co-administered with itraconazole; average olaparib C_{max} and AUC are decreased by ~60% and 80%, respectively if co-administered with rifampicin. It is recommended that patients requiring medication with known potent inhibitors or inducers of CYP3A4 are not treated with olaparib.
- In vitro data have shown that olaparib is a substrate for multi-drug resistant protein (MDR) 1, but drug interactions with inhibitors of MDR1 are considered unlikely. Weak inhibition of breast cancer resistance protein (BCRP) was shown in vitro, but at the exposures achieved following a 400 mg bd dose, drug interactions with BCRP substrates are considered unlikely. Olaparib inhibited both organic cation transporter (OCT) 1 and organic anion-transporting polypeptide (OATP) 1B1 in vitro suggesting that drug interactions with substrates of these transporter proteins (eg, metformin, statins) are possible. Clinical studies to investigate the magnitude of such an interaction have not been performed, but evaluation of the tolerability data from the clinical program do not suggest any potentiation of the commonly reported adverse events associated with metformin or statin use when given concurrently with olaparib.

- Inhibition of PARP-1 activity has been demonstrated in peripheral blood mononuclear cells (PBMC) and tumor samples from patients dosed with olaparib at all dose levels studied (10 mg to 600 mg) but the data show wide inter-subject variability in the extent of inhibition achieved and has not been used in dose selection.
- Population analysis indicated no relationships between plasma exposure to olaparib and activity endpoints (cancer antigen [CA]-125 response, change in tumor size, tumor response) or the olaparib adverse events explored.
- Interim data, available from 44 patients from 2 ongoing clinical studies, have shown that when olaparib was dosed as a monotherapy, both as a single dose (100 or 300 mg tablet formulation) and after multiple dosing at 300 mg bd, no effect on QT interval was observed.

3. OLAPARIB CLINICAL DEVELOPMENT PROGRAM

3.1 Regulatory history

Consultations with FDA regarding the olaparib ovarian cancer program were initiated in November 2009 with the most recent meeting held on 02 October 2013 ([Table 2](#)) and NDA submission on 03 February 2014.

Table 2 Summary of key regulatory interactions

Date	Communication
23 October 2012	Type C meeting to discuss the olaparib development program for patients with <i>gBRCAm</i> ovarian cancer. Study Design for SOLO2, the confirmatory Phase III platinum sensitive relapse maintenance study, was discussed.
18 March 2013	AstraZeneca and Myriad met with CDRH to discuss the framework for a pre-market approval of the companion diagnostic.
15 May 2013	FDA informed AstraZeneca that it would be acceptable to base an NDA upon Study 19 for review under subpart H, to obtain accelerated approval.
02 October 2013	AstraZeneca and FDA discussed the content of the NDA that lead to the review of this application.
07 October 2013	Confirmation of Chemistry Manufacturing and Control (CMC) technical content for NDA
16 October 2013	Orphan Drug Designation granted for ovarian cancer.

Table 2 **Summary of key regulatory interactions**

Date	Communication
03 February 2014	NDA submission filed
25 February 2014	AstraZeneca and Myriad met with FDA Center for Devices and Radiological Health (CDRH) and Center for Drug Evaluation and Research (CDER) to address challenges to the timely submission of a PMA (pre-market approval) to be contemporaneous with the NDA approval.

In addition, a European Marketing Authorization Application (MAA) was submitted in September 2013 for olaparib as maintenance treatment of adult patients with PSR *BRCAm* ovarian cancer (including fallopian tube or primary peritoneal) who are in response (complete response or partial response) to platinum-based chemotherapy. Interactions are ongoing with the European authorities.

***BRCA* mutation status testing**

In the US, commercial testing for germline *BRCA* (*gBRCA*) mutations is offered by a number of organizations. Myriad Genetics Laboratories Inc. has offered a laboratory developed test (LDT) for determination of *BRCA* related hereditary breast and ovarian cancer risk since 1994. To date Myriad has conducted more than 1 million tests and currently deliver approximately 150,000 *BRCA* tests per year.

AstraZeneca is working with Myriad to deliver a Pre-Market Approval (PMA) for the Integrated BRACAnalysis[®] assay as a companion diagnostic to olaparib. This is being undertaken in accordance with the FDA draft guidance on companion diagnostic development that was issued on 14 July 2011. AstraZeneca and Myriad have conducted Pre-Submission meetings with CDRH to discuss the regulatory approval path for the companion diagnostic and continue to work with FDA on the PMA submission. The PMA submission is being undertaken in a modular fashion, which commenced in December 2013. Submission of the final module is scheduled for July 2014. All patients enrolled on the phase III trials will be tested with the Integrated BRACAnalysis[®] test. An Investigational Device Exemption for the Integrated BRACAnalysis[®] was granted in full on 23 August 2013 to support the ongoing phase III clinical studies.

3.2 Clinical dose selection

3.2.1 400 mg bd capsule formulation

The recommended dose is 400 mg (eight 50 mg capsules) taken twice daily (bd), administered continuously until disease progression. This dose was shown to be effective, tolerable and suitable for long-term maintenance therapy. The 400 mg bd dose is delivered by eight capsules, administered twice daily.

The clinical efficacy of olaparib appears to be dose dependent. However, exposure ($C_{max ss}$ and AUC_{ss}) following a dose of 400 mg bd is not markedly different to that following a 100 mg bd or a 200 mg bd dose and inter-patient variability within any given dose level was high. In addition, the clinical PKPD relationship, using PARP inhibition in peripheral blood mononuclear cell (PBMC) and tumor samples, was not predictive of the dose required to achieve efficacy. Therefore, the dose selection for the olaparib program was based primarily on measures of efficacy in the Phase I/II monotherapy trials.

Although simple analysis of PARP inhibition in PBMCs is not predictive of efficacy, modeling based on maintaining concentrations above IC_{90} for the dosing interval does provide evidence supporting the dose selection of 400 mg bd. Pre-clinical PKPD modeling and simulation suggest that doses (in mouse) which result in tumor regression are those which deliver free plasma concentrations above the IC_{90} for tumor PARP inhibition for a period of >6 hours and predicts that a significant increase in DNA SSBs occurs only once the IC_{90} for PARP inhibition has been achieved. Further evaluation of the clinical exposure data has been conducted to compare the geometric mean free steady state trough plasma concentration ($\pm 90\%$ CI) with the estimated pre-clinical IC_{90} value (and its 95% CI). This analysis has shown that a 400 mg bd capsule dose would be expected to maintain plasma concentrations above the IC_{90} (and its upper 95% CI) across the full dosing interval. In contrast, a dose of 200 mg bd would be expected to deliver a plasma concentration above the IC_{90} in most but not all patients whilst following a dose of 100 mg bd the plasma concentrations achieved in the majority of patients would be lower than the IC_{90} . The outcome of this analysis is consistent with the clinical efficacy data obtained and supports the choice of the 400 mg bd dose.

The olaparib 400 mg bd capsule dose consistently demonstrates numerically favorable efficacy in terms of objective response rate (ORR), mean best percentage change in tumor size, and PFS, compared with olaparib 200 mg bd or 100 mg bd in both breast cancer and ovarian cancer populations ([Table 3](#)).

Table 3 Summary of objective response rate (ORR), percentage change in tumor size and median PFS for dose selection

	Study 08 (Phase II <i>gBRCA</i> breast proof of concept study)		Study 09 (Phase II <i>gBRCA</i> ovarian proof of concept study)		Study 12 (Phase II <i>gBRCA</i> ovarian monotherapy dose finding study)	
	Olaparib 100 mg bd (N=27)	Olaparib 400 mg bd (N=27)	Olaparib 100 mg bd (N=24)	Olaparib 400 mg bd (N=33)	Olaparib 200 mg bd (N=32)	Olaparib 400 mg bd (N=32)
RECIST ORR (%)	22	41	13	33	25	31
Mean best percentage change in tumor size (%)	1	-36	-5	-26	-16	-24
Median PFS (months)	3.8	5.7	1.9	5.8	6.5	8.8

Of all the patients exposed to olaparib monotherapy capsules in AstraZeneca-sponsored studies (estimated 962), the majority (735) have received the 400 mg bd dose. Study 02 (the

Phase I first time in man study) showed that the maximum tolerated dose (MTD) of olaparib was 400 mg bd administered on a continuous basis, and all olaparib monotherapy studies conducted before Study 19 indicated that olaparib monotherapy was generally well tolerated at doses up to and including the MTD.

3.2.2 300 mg bd tablet formulation

An oral tablet formulation of olaparib has been developed and is being used in all phase III studies, including the confirmatory phase III study (SOLO2). The recommended tablet dose is 300 mg bd. The tablet formulation contains 100 mg or 150 mg of olaparib, providing a convenience benefit to patients in terms of smaller number of tablets administered daily, compared to number of capsules.

The capsule and tablet formulation are not bioequivalent. Study 24, a dose ranging study in patients with advanced *gBRCA* mutated ovarian cancer, was therefore designed to match the tablet to the 400 mg bd capsule dose in terms of efficacy and tolerability. Study 24 tested a number of different doses and schedules, including twice daily (bd), three times daily and intermittent schedules. The 300 mg bd tablet dose was selected as the dose/schedule for phase III on the basis of efficacy and safety data from Study 24:

- Mean % change in tumor size from baseline was numerically similar between the 300 mg bd tablet dose and the 400 mg bd capsule dose (Table 4).
- Tolerability of the 300 mg bd tablet was similar to the 400 mg bd capsule (Table 5).

Table 4 Tumor shrinkage in 300 mg bd tablet dose vs 400 mg capsule dose in patients with advanced *gBRCAm* ovarian cancer – Study 24

	Adjusted mean tumor shrinkage (%)		Treatment effect: difference in mean tumor shrinkage (300 mg bd tablet vs 400 mg bd capsule)
	300 mg bd tablet (n=13)	400 mg bd capsule (n=20)	
Week 8	-20.1	-19.4	-0.7 (95% CI -18.9-17.4)

Adjusted for baseline tumor size, platinum sensitivity, number of prior chemotherapy regimens and peritoneal involvement at baseline.
A difference in means of <0 favors the 300 mg bd tablet.

Table 5 Tolerability of the 300 mg bd tablet dose vs 400 mg bd capsule dose - Study 24

	300 mg bd tablet (n=13)		400 mg bd capsule (n=20)	
	% All grades	% Grade ≥3	% All grades	% Grade ≥3

AE

Table 5 Tolerability of the 300 mg bd tablet dose vs 400 mg bd capsule dose - Study 24

	300 mg bd tablet (n=13)		400 mg bd capsule (n=20)	
	% All grades	% Grade ≥3	% All grades	% Grade ≥3
Nausea	69	0	90	5
Vomiting	38	0	30	5
Fatigue	62	15	55	5
Anemia	38	23	15	10
Any SAE	22		21	

Nausea and vomiting were reported with both formulations, with nausea being grade 1/2 in all but one case (grade 3). Of note 31% of the tablet patients entered the study with a current medical history of nausea compared with only 5% of the capsule patients. Whilst there appeared to be a higher reporting incidence of fatigue and anemia in the tablet cohort, 4/13 (31%) patients receiving tablet entered the study with a current medical history of anemia compared with only 1 patient receiving capsule, and 6/13 tablet patients entered with fatigue compared to 5/20 capsule patients. SAEs were reported in a similar proportion of patients for tablet vs capsule.

On the basis of these efficacy and safety findings in Study 24, the 300 mg bd tablet dose was selected for the phase III program.

3.3 Study 19: the pivotal study of olaparib as maintenance treatment in platinum sensitive relapsed ovarian cancer

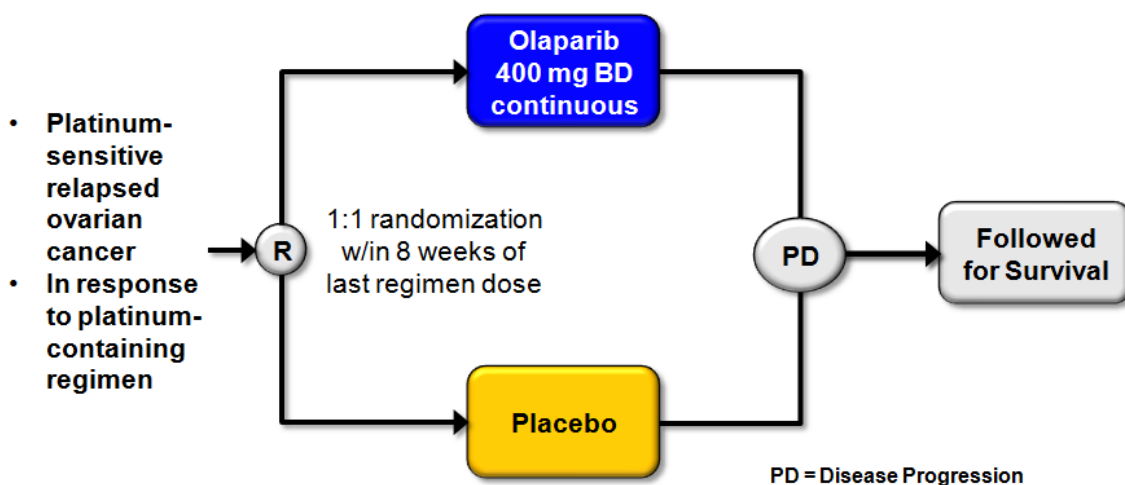
Study 19 was a randomized, double blind, multicentre study in patients with advanced high grade serous ovarian cancer, including fallopian tube or primary peritoneal carcinomas. The disease had to be platinum sensitive, ie relapsing >6 months after completion of the patient's penultimate platinum regimen. Patients had to have received 2 or more previous platinum containing regimens, the last one with at least 4 cycles. An objective response (complete response or partial response) to their last platinum-based chemotherapy regimen was required to be sustained at study entry. Patients from 82 sites in 16 countries were randomized within 8 weeks of completion of their final dose of a platinum containing regimen in a 1:1 ratio, to receive either olaparib 400 mg bd (n=136) or matching placebo bd (n=129). The first and last patients were enrolled 28 August 2008 and 09 February 2010, respectively and 44 were enrolled in the US (23 of whom were randomized to olaparib). The study is currently ongoing. The planned final event-driven 85% overall survival analysis is not expected to occur before 2016

The primary objective was to determine the efficacy of olaparib compared with placebo in the overall population, as assessed by PFS (investigator assessment). A retrospective blinded

independent central review (BICR) of scans was performed as a sensitivity analysis to confirm the robustness of the primary PFS analysis.

Secondary endpoints included overall survival (OS), best objective response (by RECIST), objective response rate (ORR), CA-125 and/or RECIST response, time to progression by CA-125 or RECIST, health-related quality of life (HRQoL), safety and tolerability.

Figure 3 Study 19 overview



3.3.1 Dose reductions and interruptions

Toxicity observed during the course of the study was managed by interruption of the dose if deemed appropriate by the Investigator. Repeat dose interruptions were allowed as required, for a maximum of 4 weeks per occurrence. Study treatment was interrupted until complete recovery or the toxicity reverted to grade 1 or less by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 3). By exception, leukopenia and/or anemia were managed as deemed appropriate by the investigator (growth factor, transfusions) without interruption or change in dose. Re-occurrence of toxicity following rechallenge led to further dose interruptions, dose reduction or permanent discontinuation.

Any treatment-related grade 3 or 4 toxicity led to temporary treatment interruption. If not resolved to grade <1 within 28 days, or by two dose reductions (to 200 mg then no less than 100 mg bd), then study treatment was discontinued.

3.3.2 Schedule of assessments

Tumor evaluation using RECIST was conducted within 28 days before first dose of study medication, every 12 weeks up to 60 weeks, then every 24 weeks until objective disease progression. Disease progression was determined by RECIST only, after which patients were

followed for safety and survival. To confirm a partial response (PR) or complete response (CR) by RECIST, a repeat scan was mandated at least ≥ 4 weeks later.

There was no maximum duration of study treatment. Patients continued blinded study treatment until progression (RECIST) or for as long as the Investigator considered there to be continued benefit. However, if patients discontinued from randomized treatment for reasons other than progression, they were to be followed for confirmed progressive disease (RECIST) and survival according to the study schedule, unless consent was withdrawn.

No cross over to olaparib was permitted within the study, although subsequent treatment (including investigational PARP inhibitors other than olaparib) was at the discretion of the investigator once patients discontinued study treatment. Patients and investigators were not routinely unblinded to study treatment, and will not be unblinded prior to the final OS analysis, which is not expected to occur before 2016. Unblinding was only permitted if knowledge of the treatment assignment was necessary for the management of medical emergencies, or the patient was considered for enrolment into another study in which prior PARP inhibitor therapy was not allowed.

At the time of the primary PFS analysis, 35 patients (8 and 27 in the olaparib and placebo groups, respectively) were unblinded. Of the 8 patients in the olaparib group, 1 patient was unblinded prior to RECIST progression and 7 were after RECIST progression. Of the 27 patients in the placebo group, 4 patients were unblinded without RECIST progression and 23 patients were after RECIST progression. Since most (30/35; 86%) of the unblindings occurred post progression, they were not considered to have affected the primary efficacy analysis. Results were confirmed by BICR, which was blinded to assignments in all patients. Safety seemed not associated to unblinding, since 73% of placebo treated patients had an AE deemed to be causally related to study treatment.

3.3.3 Statistical methods and considerations

The primary analysis used progression-free survival (PFS) programmatically derived from the target lesion measurements, non-target and new lesion assessments recorded by the investigators with an event-driven data collection cut-off (DCO) 30 June 2010. Protocol-mandated routine imaging assessments for progression were no longer required after this data cut-off. The effect of treatment was estimated by the adjusted hazard ratio (HR) with 95% confidence intervals (CIs). Kaplan-Meier plots of PFS were presented by treatment group. Cox proportional hazard was adjusted for: (i) time to disease progression from completion of penultimate platinum-containing therapy (last dose) prior to enrolment on the study (>6 to ≤ 12 months vs >12 months), (ii) objective response to last platinum-containing regimen prior to enrolment on the study (CR vs PR), and (iii) ethnic descent (Jewish vs non-Jewish). If the observed p-value for the treatment difference was <0.025 (1 sided) then the result was regarded as statistically significant. In addition to the BICR, sensitivity analyses were performed to rule out bias resulting from different timing of scans between arms and the extent and timing of censoring (see Section 9, Appendix 1). Subgroup analyses according to *BRCA* mutation status, along with other subgroups, were pre-defined in the Statistical Analysis Plan. A global interaction test was performed to test for consistency across all

subgroups defined by the stratification factors, plus *BRCA* mutation status. The investigation of subgroups was performed to assess whether some groups of patients benefited more than others, and represents standard scientific practice in the context of an overall positive study.

An event-driven formal interim analysis of OS was performed at 58% maturity (154 deaths in 265 patients randomized) with a data cut-off (DCO) of 26 November 2012. Presented in this briefing book are updated safety analyses and efficacy analyses using this DCO, including an exploratory analysis of time from randomization to second subsequent therapy or death (TSST), to provide reassurance that olaparib maintenance therapy did not adversely affect sensitivity to subsequent chemotherapy.

No adjustments were made for multiplicity introduced by analyzing multiple secondary and exploratory endpoints (excluding OS), or analyses within the *BRCA* subgroups. Control of type I error for the exploratory endpoints, including time to second subsequent therapy or death (TSST) was not defined in this phase II study. As such, where p-values <0.05 are observed for these endpoints (meeting nominal significance), statistical significance is stated. In October 2012, the protocol was amended and the OS analysis at 58% maturity was classed as a subsequent interim analysis with a final analysis planned to occur at approximately 85% maturity. This amendment detailed the change to the multiplicity adjustment in order to continue controlling the overall alpha at 2.5% (1-sided).

Regarding health-related quality of life (HRQoL), for each trial outcome index endpoint (TOI; the primary endpoint for HRQoL), FACT/NCCN ovarian symptom index (FOSI) and total functional analysis of cancer therapy - ovarian (FACT-O), the proportion of patients with best responses of 'Improved', 'No Change' and "Worsened" were compared between treatments using logistic regression with factors as for the analysis of PFS. The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O, using a Cox proportional hazards model using the same factors as for the analysis of PFS. The association between HRQoL/symptom response (TOI, FACT-O, FOSI) and RECIST response were assessed through cross tabulation of the 2 response categories. These data are presented as of the DCO of 30 June 2010.

3.3.4 Analysis populations and patient disposition

Efficacy was primarily assessed in the intent to treat population. In addition, an analysis of efficacy by *BRCA* mutation status was pre-specified in the SAP prior to unblinding of data.

At the time of the initial primary analysis, *gBRCA* mutation status had been prospectively recorded on CRFs at study entry for 59 patients (31 in the olaparib arm vs 28 in the placebo arm). However, following blinded retrospective testing, *BRCA* mutation status is now known for 96% (254/265) of all patients in Study 19 by blood and or tumor testing. In total, 96 patients

Table 6 Analysis sets in Study 19

Analysis set	Brief description	Olaparib 400 mg bd	Placebo	Total
Intent to treat (ITT)	All patients, irrespective of <i>BRCA</i> mutation status	136	129	265
Safety Analysis	All patients who received randomized study treatment	136	128	264 ^a
Germline <i>BRCA</i> mutated (<i>gBRCAm</i>)	Patients with a <i>BRCA</i> mutation identified in the germline	53	43	96
<i>gBRCA</i> wildtype/VUS ^b (<i>gBRCAwt/VUS</i>)	Patients without <i>gBRCA</i> mutation (or a variant of unknown clinical significance)	50	64	114
<i>gBRCA</i> missing	Patients for whom <i>gBRCA</i> mutation status is unknown	23	22	55

a One patient withdrew consent before receiving any study treatment.

b Wildtype/VUS (variant of unknown significance) indicates patients without known deleterious *BRCA* mutation.

Patient disposition is summarized for ITT and the *gBRCA* subgroup in Table 7. For the subpopulation of patients with a *gBRCA* mutation, all 96 patients received study treatment: 53 patients were randomized to olaparib and 43 to placebo. Similar to the observations in the overall population and the *BRCAm* subgroup, the majority of patients (65/84 [77%]) with a *gBRCA* mutation who discontinued study treatment did so due to worsening of the condition under investigation.

Table 7 Disposition of patients in Study 19

	Number (%) of patients					
	ITT			<i>gBRCAm</i>		
	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265	Olaparib 400 mg bd n=53	Placebo n=43	Total n=96
Patients ongoing study treatment at data cut-off (26 November 2012)	23 (17)	3 (2)	26 (10)	10 (19)	2 (5)	12 (13)
Patients who discontinued study treatment	113 (83)	125 (98)	238 (90)	43 (81)	41 (95)	84 (88)
Adverse event	6 (4)	2 (2)	8 (3)	4 (8)	0	4 (4)
Condition under investigation worsened	87 (64)	110 (86)	197 (75)	29 (55)	36 (84)	65 (68)

Table 7 **Disposition of patients in Study 19**

	Number (%) of patients					
	ITT			<i>gBRCAm</i>		
	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265	Olaparib 400 mg bd n=53	Placebo n=43	Total n=96
Severe non-compliance to protocol	2 (2)	1 (1)	3 (1)	0	1 (2)	1 (1)
Patient lost to follow-up	1 (1)	0	1 (<1)	0	0	0
Voluntary discontinuation by patient	11 (8)	8 (6)	19 (7)	7 (13)	3 (7)	10 (10)
Other	6 (4)	4 (3)	10 (4)	3 (6)	1 (2)	4 (4)
Patients ongoing study	46 (34)	42 (33)	88 (33)	20 (38)	16 (37)	36 (38)
Patients who terminated study	90 (66)	87 (67)	177 (67)	33 (62)	27 (63)	60 (63)
Death	77 (57)	77 (60)	154 (58)	27 (51)	22 (51)	49 (51)
Patient lost to follow-up	5 (4)	5 (4)	10 (4)	1 (2)	3 (7)	4 (4)
Voluntary discontinuation of patient	8 (6)	5 (4)	13 (5)	5 (9)	2 (5)	7 (7)

3.3.5 Study population

Overall, the population of patients who participated in this study was typical of the intended study population (ie, patients with platinum-sensitive relapsed high-grade serous ovarian cancer, including fallopian tube or primary peritoneal). Demographic and baseline patient characteristics were similar for the overall population and the *gBRCAm* subgroup (Table 8). Baseline characteristics for the intent to treat (ITT) population are summarized in Table 34 and Table 35 in the appendices.

In the *gBRCAm* population, the treatment groups were generally well balanced across the stratification factors of previous response to platinum treatment (covariate defined using presence of disease at baseline; presence = PR, absence = CR). Slight imbalances were noted between treatment arms in the number of patients of Jewish descent and platinum sensitivity (ie, time to disease progression from completion of the penultimate platinum-containing prior to enrolment on the study). These imbalances are not considered to unduly affect study analyses. The primary analysis method adjusted for these factors as covariates and additional analyses confirm that any imbalances in baseline factors do not alter the conclusions.

Table 8 **Summary of baseline demographic and patient characteristics in patients with *gBRCA* mutations – Study 19**

	Number (%) of patients		
	Olaparib 400 mg bd (n=53)	Placebo (n=43)	Total (n=96)
Age Median (years)	56	55	56
Age ≥65 years	29 (55)	24 (56)	53 (55)
Race, n (%)			
White	49 (93)	42 (98)	91 (95)
Black/African American	2 (4)	0	2 (2)
Asian	1 (2)	1 (2)	2 (2)
Other	1 (2)	0	1 (1)
Ethnic population, n (%)			
Jewish descent			
No	43 (81)	31 (72)	74 (77)
Yes	10 (19)	12 (28)	22 (23)
Ashkenazi Jewish	10 (19)	9 (21)	19 (20)
ECOG performance status, n (%)			
(0/1) Normal/restricted activity	52 (98)	42 (98)	94 (98)
(2) In bed ≤50% of the time	0	1 (2)	1 (1)
Unknown	1 (2)	0	1 (1)
Primary tumor location			
Ovary	47 (89)	37 (86)	84 (88)
Fallopian Tube	1 (2)	1 (2)	2 (2)
Primary peritoneal	5 (9)	5 (12)	10 (10)
Tumor grade			
Well Differentiated	0	0	0
Moderately Differentiated	12 (23)	11 (26)	23 (24)
Poorly Differentiated	39 (74)	31 (72)	70 (73)
Undifferentiated	1 (2)	0	1 (1)
Unassessable	1 (2)	1 (2)	2 (2)
Platinum sensitivity			
>6 to ≤12 months	22 (42)	21 (49)	43 (45)
>12 months	31 (59)	22 (51)	53 (55)
Objective response to last platinum regimen			
Complete response (PR)	29 (55)	22 (51)	51 (53)
Partial response (PR)	24 (45)	21 (49)	45 (47)

3.4 Study 19: key efficacy data

- To best inform the proposed indication under review, while taking into account that the proposed companion diagnostic is a blood-based test (Myriad Integrated BRACAnalysis[®]), efficacy presentations will focus on the patient subgroup detected by the blood test (*gBRCA* mutated patients). This is consistent with FDA guidance for this application. Intent-to-treat (ITT) analyses are presented where appropriate to demonstrate the overall positive nature of the study, enabling more detailed consideration of the population predicted by the biology and study design to experience greater benefit with equivalent risk profile.
- Study 19 met its primary endpoint of significantly prolonging PFS with maintenance treatment with olaparib vs placebo (HR 0.35; 95% CI 0.25-0.49; $p < 0.00001$; median 8.4 months vs 4.8 months; assessed by investigators; 58% maturity; DCO 30 June 2010) based on 154 PFS events in 265 patients (ITT population).
- Sensitivity analyses for evaluation time and attrition bias were consistent with the primary analysis (HR 0.39 and 0.35, respectively). The statistical analysis of PFS by blinded independent central review (HR 0.39; 95% CI 0.28-0.56; $p < 0.00001$) confirmed the robustness of the investigator assessment.
 - The Kaplan-Meier plot for the primary analysis of PFS in the ITT population is shown in [Figure 4](#)
 - A Forest plot of the sensitivity analyses for the ITT population is shown in [Figure 5](#).
 - Section 9 in the appendices presents further results and details of the analyses undertaken, which confirm the robustness of the PFS analysis.
- All subsequent subgroup analyses, including the *gBRCA* subgroup, were therefore conducted in the context of an overall positive study.

Figure 4 PFS in the ITT population – Study 19

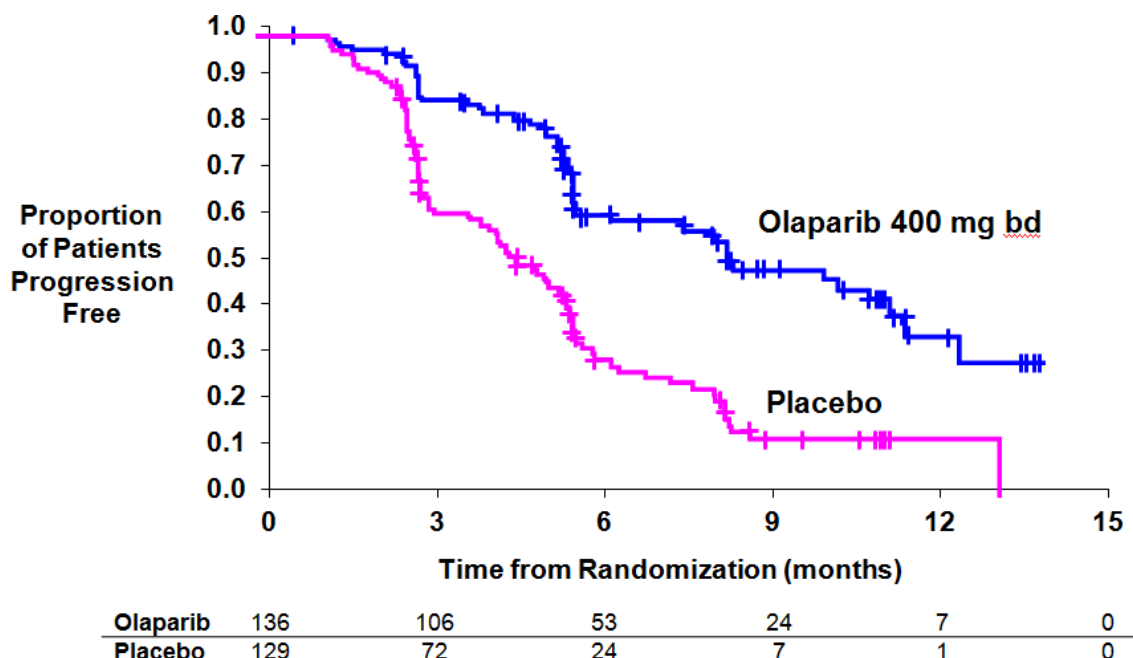
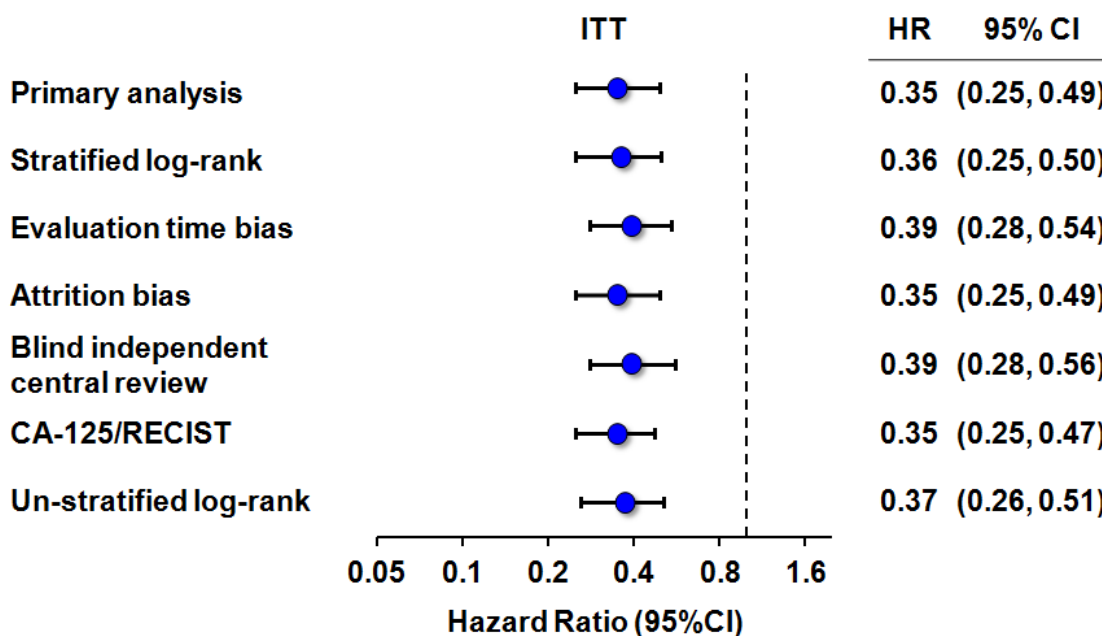


Figure 5 Sensitivity analyses for PFS in the ITT population –Study 19



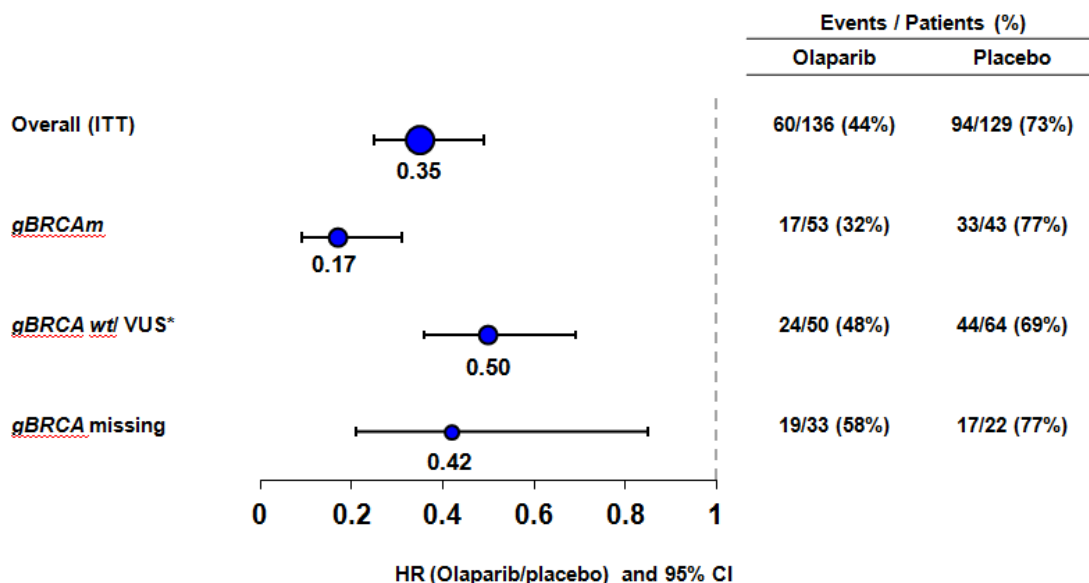
The predicted greater benefit in patients with a *gBRCA* mutation was initially confirmed in the 59 patients who had, per study protocol, their mutation status documented prospectively on CRFs at screening from local testing (PFS HR 0.11; 95% CI 0.04-0.27; $p < 0.00001$).

- Retrospective testing was then undertaken for all patients for whom suitable blood/tumor samples and consent were available, and *BRCA* mutation status was ultimately confirmed in 96% of all patients, of whom 96 patients had germline mutation confirmed by a blood test (the *gBRCAm* subgroup).
- As predicted by the biology, greater benefits are seen in the subgroup of 96 patients with *gBRCA* mutations compared with the overall study population or the complement subgroups (Figure 6):
 - In the *gBRCAm* subgroup (n=96): PFS HR=0.17; 95%CI 0.09-0.31; p<0.00001; median 11.2 months vs 4.1 months in the olaparib vs placebo arms, respectively.
 - In the *gBRCAwt/VUS* subgroup (n=114): PFS HR=0.50; 95%CI 0.29-0.82; p=0.00572; median 8.3 months vs 5.5 months in the olaparib vs placebo arms, respectively.
 - In the *gBRCA* missing subgroup (n=55): PFS HR=0.43; 95%CI 0.21-0.87; p=0.01970; median 7.4 months vs 4.5 months in the olaparib vs placebo arms, respectively.
- The benefit seen in the ITT and wildtype/VUS and missing groups reflect the fact that the entire study population was enriched by platinum sensitivity for the HRD phenotype.
- PFS findings were also consistent in the larger subgroup (n=136) of all patients with *BRCA* mutations determined by blood and/or tumor testing (HR 0.18; 95% CI 0.10-0.31; p<0.00001; median 11.2 months vs 4.3 months). This represents a 6.9 month benefit in terms of median progression in favor of olaparib over placebo.

Table 9 Progression-free survival (PFS) - Study 19

	ITT (n=265)		<i>gBRCAm</i> (n=96)	
	Olaparib	Placebo	Olaparib	Placebo
No events: No patients (%)	60:136 (44%)	94:129 (73%)	17:53 (32%)	33:43 (77%)
Median time (months)	8.4	4.8	11.2	4.1
HR (95% CI)	0.35 (0.25–0.49)		0.17 (0.09-0.31)	
P value (2-sided)	p<0.00001		p<0.00001	

Figure 6 PFS by *gBRCA* subgroup – Study 19



gBRCA wt/ VUS = *gBRCA* wildtype or a *BRCA* mutation of unknown significance (variant of unknown significance).

- [Figure 7](#) shows the Kaplan-Meier plot for PFS in the subgroup of *gBRCAm* patients from Study 19, with an early and sustained separation of the two curves. The PFS effect corresponds to an 83% reduction in the risk of disease progression or death in patients with *gBRCAm* ovarian cancer treated with maintenance olaparib vs placebo.
- The median PFS for olaparib treated patients was 7.1 months longer than that observed in placebo treated.
- The investigator-assessed PFS benefit was confirmed by independent blinded central radiological review (PFS HR 0.25; 95% CI 0.13-0.49; $p=0.00003$; 41 events in 95 patients).
- As with the ITT population, all sensitivity analyses were supportive of the primary finding for PFS in the *gBRCA* subgroup ([Figure 8](#)).

Figure 7 PFS in patients with a *gBRCA* mutation – Study 19

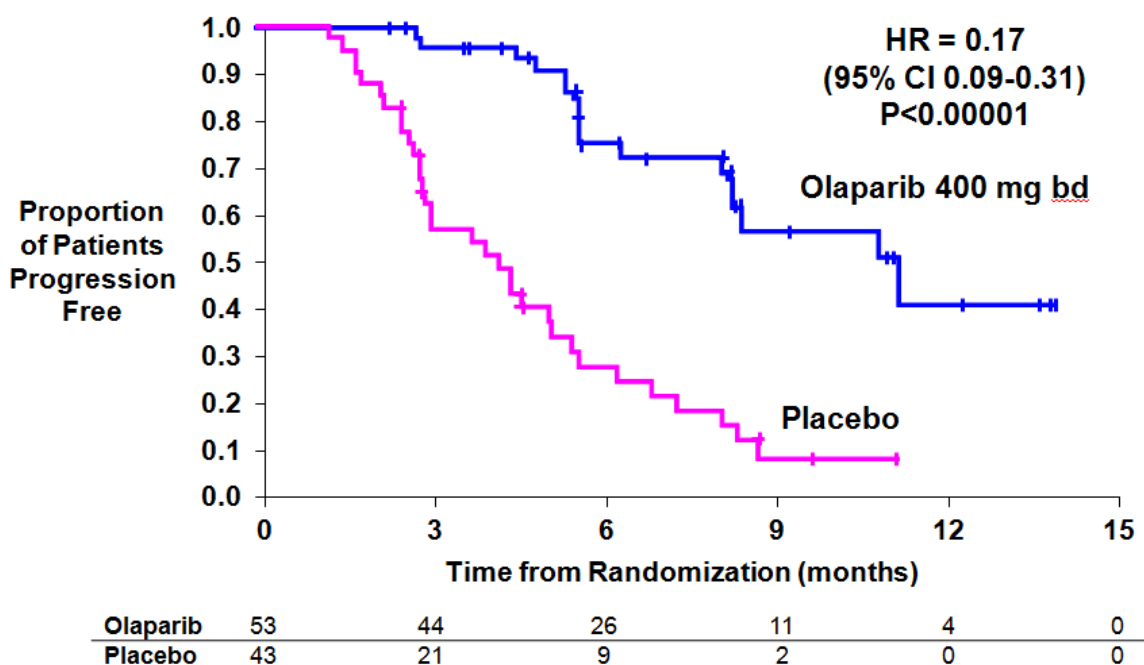
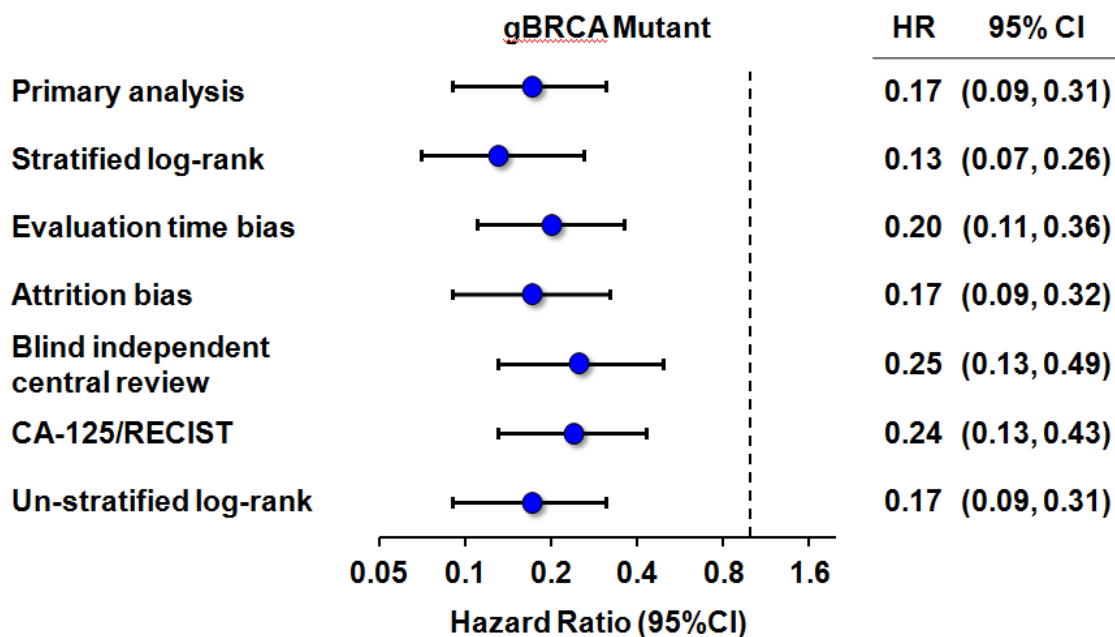


Figure 8 Sensitivity analyses for PFS in the *gBRCA* subgroup – Study 19



Exploratory analysis of time from randomization to second subsequent progression or death (TSST)

- Only patients who received a randomized treatment were able to discontinue and thus have subsequent therapies. Therefore TSST is analyzed in the Safety Analysis (n=264) rather than the ITT (n=265).
- In both the Safety Analysis population, the *gBRCA* subgroup and its complement subgroups, the analysis of TSST indicates that olaparib has no detrimental impact on the efficacy of subsequent therapies received after olaparib maintenance treatment (Table 10).
 - In the *gBRCAm* subgroup, olaparib extended median TSST by 7 months over placebo. The Kaplan Meier plot for TSST is presented for the *gBRCAm* subgroup in Figure 9 in the appendices.
 - In the *gBRCAwt/VUS* subgroup (n=114): TSST HR=0.61; 95%CI 0.39-0.94; p=0.02486; median 19.7 months vs 15.2 months in the olaparib vs placebo arms, respectively.
 - In the *gBRCA* missing subgroup (n=54): TSST HR=0.60; 95%CI 0.33-1.13; p=0.11241; median 16.3 months vs 13.0 months in the olaparib vs placebo arms, respectively.
- In the *gBRCAm* subgroup, 57% vs 86% of patients received subsequent therapy in the olaparib vs placebo arms, respectively (median numbers of subsequent lines of therapy were 1 vs 2, respectively) (Table 11).

Table 10 Time from randomization to second subsequent therapy (TSST) – Study 19

	Safety Analysis (n=264)		<i>gBRCAm</i> (n=96)	
	Olaparib	Placebo	Olaparib	Placebo
No events: No patients (%)	88:136 (65%)	108:128 (84%)	29:53 (55%)	34:43 (79%)
Median time (months)	19.1	14.8	22.0	15.0
HR (95% CI)	0.53 (0.40–0.71)		0.43 (0.25-0.71)	
P value (2-sided)	p=0.00001		p=0.00099	

Figure 9 Time from randomization to second subsequent therapy or death (TSST) in patients with *gBRCA* mutation – Study 19

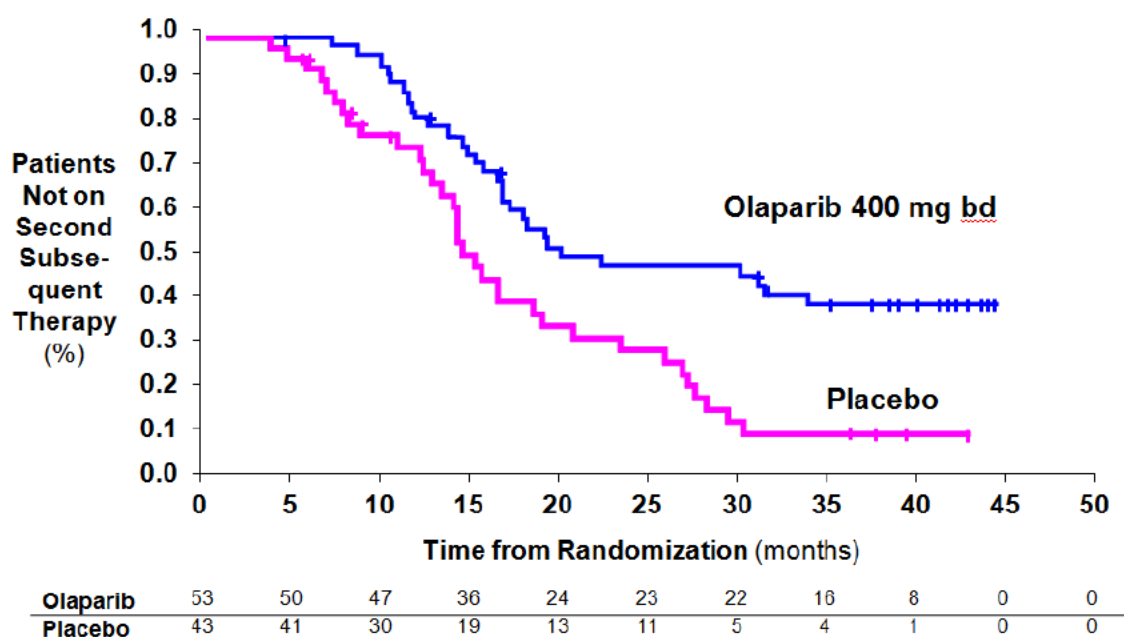


Table 11 Study 19: Summary of number of subsequent therapies and subsequent PARP inhibitor use by mutation status

	Number (%) of patients		
	Olaparib 400 mg bd	Placebo	Total
ITT			
N	136	129	265
N with ≥ 1 subsequent therapy	84 (62)	108 (84)	192 (72)
N with ≥ 2 subsequent therapies	52 (38)	76 (59)	128 (48)
N with ≥ 3 subsequent therapies	38 (28)	53 (41)	91 (34)
N with ≥ 4 subsequent therapies	19 (14)	30 (23)	49 (18)
N with ≥ 5 subsequent therapies	10 (7)	15 (12)	25 (9)
N who subsequently received a PARP inhibitor ^a	0	16 (12)	16 (6)
<i>gBRCA</i> mutation			
N	53	43	96
N with ≥ 1 subsequent therapy	30 (57)	37 (86)	67 (70)
N with ≥ 2 subsequent therapies	18 (34)	25 (58)	43 (45)
N with ≥ 3 subsequent therapies	15 (28)	16 (37)	31 (32)
N with ≥ 4 subsequent therapies	6 (11)	11 (26)	17 (18)

Table 11 **Study 19: Summary of number of subsequent therapies and subsequent PARP inhibitor use by mutation status**

	Number (%) of patients		
	Olaparib 400 mg bd	Placebo	Total
N with ≥ 5 subsequent therapies	3 (6)	4 (9)	7 (7)
N who subsequently received a PARP inhibitor ^a	0	13 (30)	13 (14)

^a As reported by the investigator
Reported therapies do not include surgery.

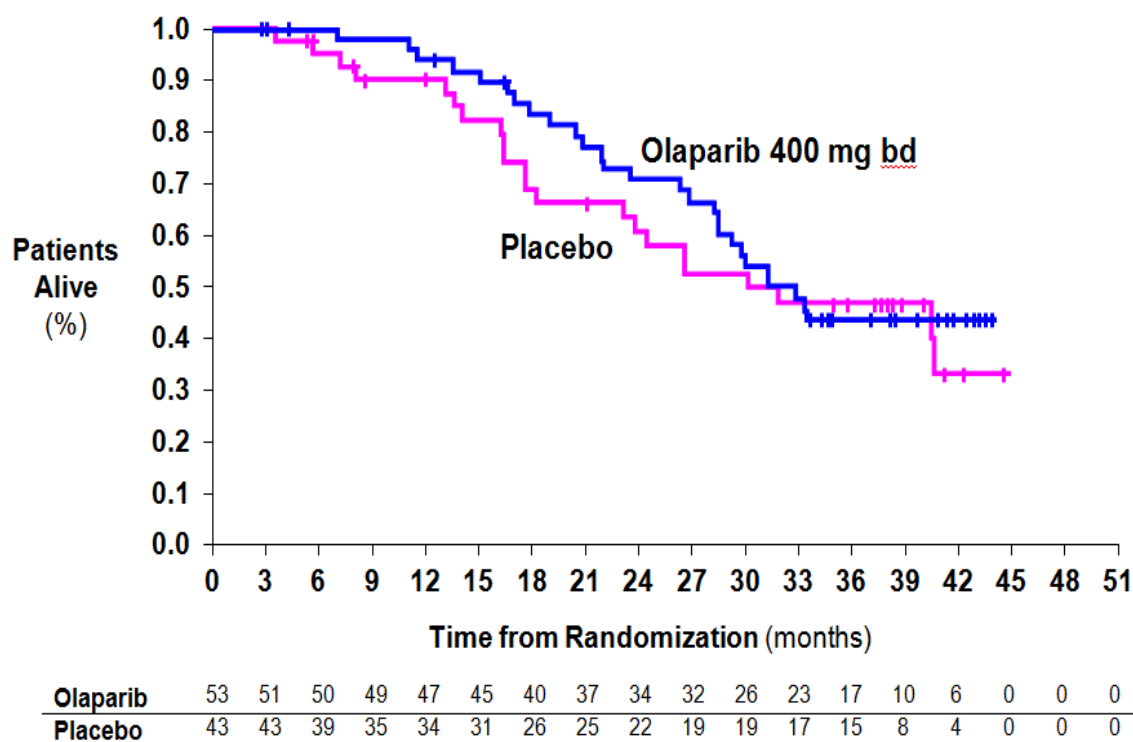
Overall survival in Study 19

- Study 19 did not demonstrate a statistically significant difference in OS. Whilst a survival benefit cannot be concluded, there is no evidence of any detriment to survival with olaparib compared with placebo.
- An interim OS analysis was prospectively planned for when the number of OS events was similar to the number of PFS events in the primary analyses (~60% maturity), to enable data assessment with a similar level of precision. The OS data was 58% mature in the overall population at the time of analysis (51% in the *gBRCAm* subgroup).
- The study did not demonstrate a statistically significant difference for OS in either the overall population or *gBRCAm* population (Table 12), or in the complement subgroups:
 - In the *gBRCAm* subgroup, a non-significant hazard ratio for death was observed for olaparib vs placebo. Of note, although no cross over was permitted during the study, approximately a third of patients randomized to placebo in the *gBRCAm* subgroup (13/43; 30%) received non-protocolled post-study treatment with a PARP inhibitor.
 - In the *gBRCAwt/VUS* subgroup (n=114): OS HR=0.86; 95%CI 0.52-1.39; p=0.54; median 29.7 months vs 29.2 months in the olaparib vs placebo arms, respectively.
 - In the *gBRCA* missing subgroup (n=55): OS HR=0.88; 95%CI 0.44-1.77; p=0.72677; median 25.4 months vs 25.9 months in the olaparib vs placebo arms, respectively.

Table 12 Overall survival (OS) - Study 19

	ITT (n=265)		<i>gBRCAm</i> (n=96)	
	Olaparib	Placebo	Olaparib	Placebo
No events: No patients (%)	77:136 (57%)	77:129 (60%)	27:53 (51%)	22:43 (51%)
Median time (months)	29.8	27.8	32.9	30.2
HR (95% CI)	0.88 (0.64–1.21)		0.85 (0.48-1.52)	
P value (2-sided)	p=0.44		p=0.58	

Figure 10 Overall survival in *gBRCAm* patients - Study 19



Health related quality of life (HRQoL)

During treatment, patient-reported HRQoL and disease-related symptoms were collected using the Functional Assessment of Cancer Therapy Ovarian (FACT-O) questionnaire. The questionnaire was administered at baseline and every 12 weeks up to 60 weeks then every 24 weeks until objective progression or the patient withdrew consent.

The Functional Assessment of Cancer Therapy – Ovarian (FACT-O) is a reliable and valid quality of life instrument for ovarian cancer patients (Basen-Engquist et al 2001) translated for use in multiple countries and languages with equivalence of meaning and measurement between different country versions established using the FACIT translation methodology (Eremenco et al 2005). There was only one participating country where a validated translation was not available, and this reason excluded 14 patients in the ITT population from the HRQoL analyses.

The main analysis of HRQoL was based on the Trial Outcomes Index (TOI), which is one of the scores derived from the FACT-O. TOI is a summary index responsive to change in physical/functional outcomes and specific concerns to ovarian cancer patients and includes a summary of physical well-being, functional well-being, and ovarian cancer additional concern scores. In addition, FACT/NCCN ovarian symptom index (FOSI), a brief 8-item index derived from the FACT-O which can measure symptom response to treatment for ovarian cancer (Beaumont et al 2007) and FACT-O total score were also analyzed.

The proportion of patients with best responses of ‘Improved’, ‘No Change’ and ‘Worsened’ were compared between treatments using logistic regression with factors as for the analysis of PFS. The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O, using a Cox proportional hazards model using the same factors as for the analysis of PFS. These data are presented as of the DCO of 30 June 2010.

HRQoL results are presented in Table 13.

Table 13 Study 19: HRQoL in evaluable patients within the ITT population and *gBRCAm* subgroups (DCO 30 June 2010)

	Evaluable patients in the ITT		Evaluable patients in the <i>gBRCAm</i> subgroup	
	Olaparib 400 mg bd	Placebo	Olaparib 400 mg bd	Placebo
TOI	n=115	n=111	n=45	n=37
Best response, %				
Improved ^a	20	18	27	8
No change ^b	63	60	60	60
Worsened ^c	14	18	9	24
Non-evaluable	4	4	4	8
Improvement rate	20% vs 18%		27% vs 8%	
OR (95% CI), P value	1.14 (0.58-2.24) p=0.69902		4.08 (1.11-19.9) p=0.03337	
Median time to worsening, months	3.8	4.6	7.4	3.6
HR (95% CI), P value	1.08 (0.75-1.55) p=0.68126		0.54 (0.30-0.99) p=0.04783	

Table 13 Study 19: HRQoL in evaluable patients within the ITT population and *gBRCAm* subgroups (DCO 30 June 2010)

	Evaluable patients in the ITT		Evaluable patients in the <i>gBRCAm</i> subgroup	
FOSI	n=117	n=115	n=45	n=37
Best response, %				
Improved ^a	17	15	26	13
No change ^b	63	64	57	59
Worsened ^c	17	18	13	23
Non-evaluable	3	3	4	5
Improvement rate	17% vs 15%		26% vs 13%	
OR (95% CI), P value	1.22 (0.60-2.51) p=0.58544		2.31 (0.75-8.10) p=0.14775	
Median time to worsening, months	2.8	3.7	3.7	3.3
HR (95% CI), P value	1.22 (0.88-1.71) p=0.22802		0.71 (0.42-1.22) p=0.21194	
FACT-O	n=114	n=111	n=45	n=37
Best response, %				
Improved ^a	21	19	29	11
No change ^b	60	57	56	51
Worsened ^c	18	22	13	32
Non-evaluable	2	3	2	5
Improvement rate	21% vs 19%		29% vs 11%	
OR (95% CI), P value	1.17 (0.60-2.27) p=0.64791		3.26 (1.00-12.9) p=0.05057	
Median time to worsening, months	2.8	4.6	3.2	3.7
HR (95% CI), P value	1.16 (0.83-1.64) p=0.39094		0.84 (0.48-1.48) p=0.54938	

FACT-O Functional Analysis of Cancer Therapy – Ovarian; ITT intent to treat; FOSI FACT/NCCN Ovarian Symptom index; HR Hazard ratio; HRQoL Health-related quality of life; OR Odds ratio; TOI Trial outcome index

a Two visit responses of 'improved' a minimum of 21 days apart without an intervening visit response of 'worsened'. Improved is defined as a change from baseline of greater than or equal to: TOI +7; FOSI +3; FACT-O +9

b Two visit responses of 'no-change' or a response of 'no change' and a response of 'improved', a minimum of 21 days apart without an intervening visit response of 'worsened'. No change is defined as a change from baseline of : TOI greater than -7 but less than +7; FOSI greater than -3 but less than +3; FACT-O greater than -9 but less than +9

c A visit of 'worsened' without a response of 'improved' or 'no change' within 21 days. Worsened is defined as a change from baseline of less than or equal to: TOI -7, FOSI -3, FACT-O -9

- Baseline HRQoL scores were high and comparable across treatment arms as patients entered the study with their ovarian cancer already in response following chemotherapy. Mean scores at baseline in *gBRCAm* patients for olaparib and placebo respectively were: FACT-O 119 vs 119 out of a maximum possible score of 156, TOI 80 vs 81 out of a maximum possible score of 104, and FOSI 26 vs 25 out of a maximum score of 32. The maximum score would occur if all questions had a response corresponding to the best QOL for each question. Compliance was approximately 80% or more in both treatment arms.

- Most patients (ITT and *gBRCAm*) had a best response of no change in TOI. In the ITT population, there were no statistically significant or clinically relevant differences between treatment groups in TOI best response or time to worsening. In patients with *gBRCAm* ovarian cancer, a statistically significantly higher proportion of patients reported a best response of improved for TOI (OR=4.08, p=0.03337), and time to worsening of TOI was also statistically significantly longer for *gBRCAm* patients receiving olaparib compared with placebo (HR=0.54, p=0.04783). However, the result should be interpreted with caution given the lower proportion of TOI ‘improved’ *gBRCAm* placebo patients when compared with the ITT placebo arm (8% and 18%, respectively).
- No statistically significant differences were observed for the ITT or the *gBRCAm* populations in HRQoL as measured by FOSI and FACT-O.
- In conclusion, olaparib maintenance therapy demonstrated no detrimental impact on HRQoL outcomes compared with placebo.

Other secondary endpoints

Other endpoints included variables derived from, change in tumor size, CA-125 or RECIST progression. However, as patients in Study 19 were already in remission at study entry based on a response to their prior platinum-based chemotherapy, there were few additional responses observed during the study itself. Where data were available, they were supportive of the primary findings in favor of olaparib over placebo, although statistical significance was generally not reached.

4. SUPPORTIVE PHASE I AND PHASE II CLINICAL STUDIES

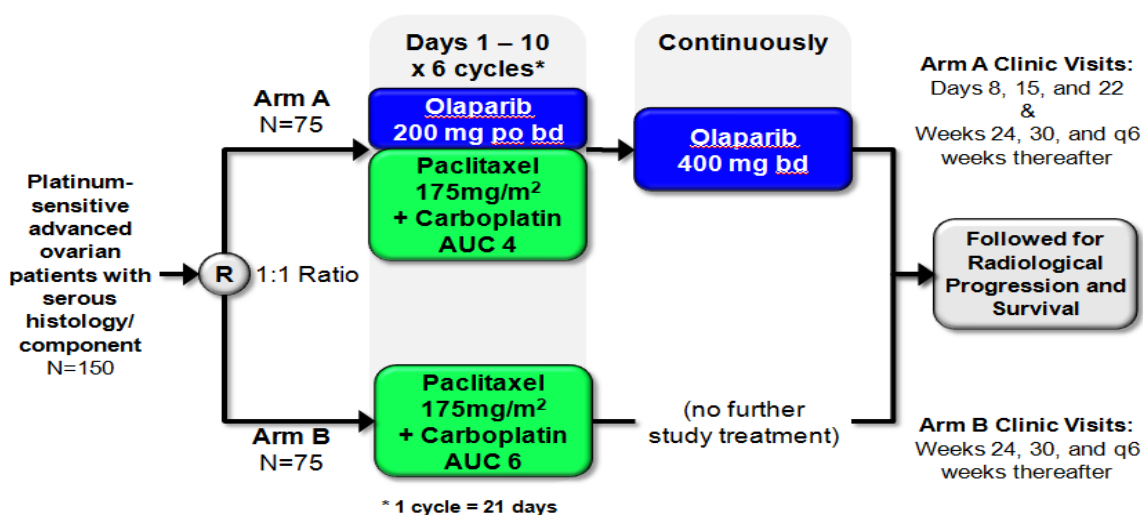
The efficacy findings of the pivotal Study 19 are supported by seven other studies in patients with *BRCA* mutations, including:

- Study 41, a randomized phase II study of olaparib in combination with chemotherapy followed by olaparib maintenance therapy in platinum-sensitive ovarian cancer. See Section 4.1.
- Study 12, a randomized phase II dose-finding study comparing efficacy of olaparib with pegylated liposomal doxorubicin (PLD) in patients with advanced *gBRCAm* ovarian cancer. PLD is a recommended standard treatment for patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy (Kaye et al 2012). See Section 4.2.
- In addition, a cross-study analysis of objective response rate in *BRCAm* ovarian cancer patients is presented in Section 4.3.
- Table 36 in the appendices provides an overview of the study designs of all 7 supportive studies.

4.1 Study 41

Study 41 was an open label randomized study testing the benefit of olaparib (200 mg bd days 1-10 of a 21-day chemotherapy cycle) in combination with paclitaxel and a reduced dose of carboplatin (AUC4) followed by olaparib administered as a continuation maintenance (400 mg bd) vs standard paclitaxel and carboplatin (dosed at AUC6) with no maintenance therapy, in patients with PSR ovarian cancer. Chemotherapy was to be continued for 6 21-day cycles (minimum 4 cycles) in order to continue into the maintenance phase of the study. If failing to achieve this requirement, patients were to receive no further study treatment, and other treatment options were at the discretion of the investigator.

Figure 11 Study 41 overview



- Knowledge of *BRCA* mutation status was not a requirement for entry into the study. At study entry, the germline *BRCA* (*gBRCA*) mutation status was known from CRFs for 35/162 patients (22%). A subgroup analysis by *BRCA* mutation status was pre-specified based on optional prospective collection of tumor samples– there was no prospective collection of blood samples for *gBRCA* mutation testing.
- Archival tumor samples were tested by next generation sequencing at Foundation Medicine, Cambridge, MA for tumor *BRCA* mutation.
 - Overall, of the 162 randomized patients, 41 patients (25%) had a *BRCA* mutation, 59 patients were identified as wildtype and 7 with a variant of unknown significance (41% non-mutated) and no information on *BRCA* mutation status was available for 55 (34%) patients.
- In Study 41, demographic and baseline characteristics were generally well balanced between treatment groups and consistent with the expected PSR population eligible for paclitaxel/carboplatin AUC6 (Table 14).

Table 14 **Baseline characteristics – Study 41 (ITT)**

	Olaparib/ carboplatin AUC4/ paclitaxel, followed by maintenance n=81	Carboplatin AUC4/ paclitaxel, no maintenance n=81	Total n=162
Age			
Median (years)	59	62	60
≥65 years, n (%)	21 (26)	24 (30)	45 (28)
Race, n (%)			
White	70 (86)	69 (85)	139 (86)
Black or African American	0	2 (3)	2 (1)
Asian	8 (10)	8 (10)	16 (10)
American Indian or Alaska Native	1 (1)	1 (1)	2 (1)
Other	2 (3)	1 (1)	3 (2)
Number of prior platinum containing treatment lines			
1	58 (72)	53 (65)	111 (69)
>1	23 (28)	28 (35)	51 (32)
Time to disease progression on completion of the previous platinum therapy			
>6 to ≤12 months	39 (48)	40 (49)	79 (49)
>12 months	42 (52)	41 (51)	83 (51)
ECOG performance status			
(0/1) Normal/restricted activity	79 (98)	78 (96)	157 (97)
(2) In bed <50% of the time	2 (3)	1 (1)	3 (2)
Missing	0	2 (3)	2 (1)

Progression-free survival in Study 41

- Study 41 was positive for the primary endpoint of PFS in the overall study population and replicated the finding of Study 19 where the treatment benefit was greatest in the population of patients with a *BRCA* mutation ([Table 15](#)).
- In the subgroup of *BRCAm* patients, there was a 79% reduction in risk of disease progression or death for olaparib treated patients in the *BRCAm* subgroup (PFS HR 0.21; 95% CI 0.08-0.55; p=0.0015; median not reached olaparib vs 9.7 months comparator arm; 23 PFS events in 41 patients).

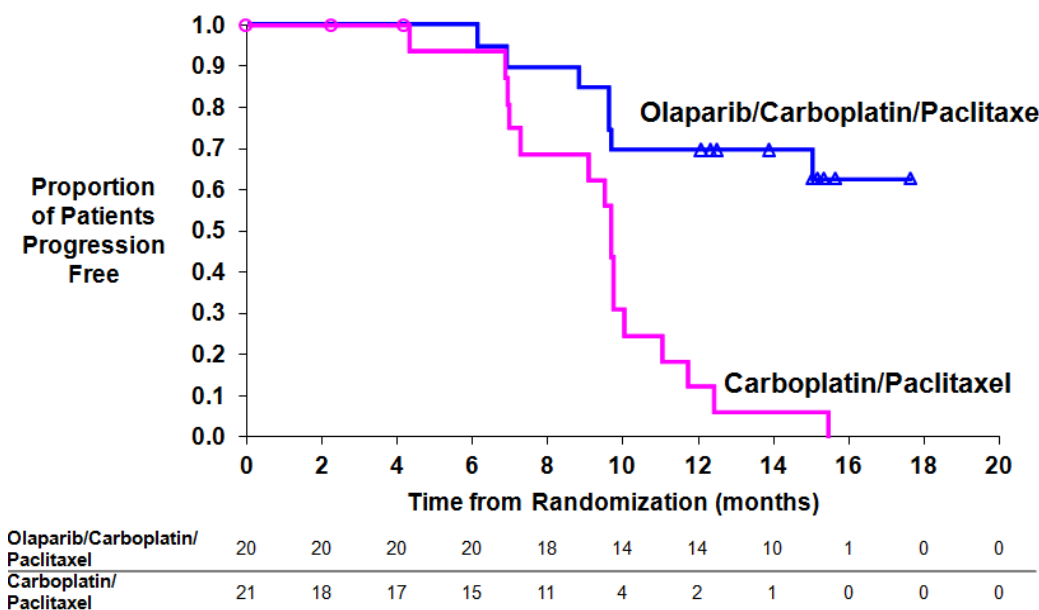
- There was no statistically significance difference in PFS between treatment arms in the *BRCA* non-mutated (wildtype/VUS) subgroup (n=66) (HR=0.77; 95% CI 0.41-1.44; p=0.4129).

Table 15 **Progression-free survival in Study 41 (DCO 10 October 2011)**

	ITT (n=162)		<i>BRCAm</i> (n=41)	
	Olaparib/ carboplatin AUC4/ paclitaxel, followed by olaparib maintenance therapy	Carboplatin AUC4/ paclitaxel, with no maintenance therapy	Olaparib/ carboplatin AUC4/ paclitaxel, followed by olaparib maintenance therapy	Carboplatin AUC4/ paclitaxel, with no maintenance therapy
No events: No patients (%)	47:81 (58%)	55:81 (68%)	7:20 (35%)	16:21 (76%)
Median time (months)	12.2	9.6	Not reached	9.7
HR (95% CI)	0.51 (0.34-0.77)		0.21 (0.08-0.55)	
P value (2-sided)	p=0.0012		p=0.0015	

- In the *BRCAm* group, the Kaplan-Meier curves separated after the completion of the chemotherapy phase when patients on the olaparib arm are receiving maintenance olaparib ([Figure 12](#)), highlighting that most of the benefit appears to be derived when olaparib is given not in combination with chemotherapy, but at a full dose as a continuation maintenance treatment.

Figure 12 PFS (independent central review) in patients with *BRCAm* ovarian cancer – Study 41



Overall survival and time from randomization to second subsequent therapy or death (TSST) in Study 41

- The final OS analysis was performed at 62% maturity (101 deaths out of 162 patients; [DCO 31 January 2014]). There was no statistically significant difference in OS between treatment arms in the ITT population or the subgroup of patients with *BRCA* mutation (Table 16).
- Patients censored early were defined as any patient who was censored for OS prior to the DCO, including patients who withdrew consent or were lost to follow-up. The number of patients who were censored early (ie, before DCO for the final OS analysis) was 1 (1.2%) in the olaparib arm and 8 (9.9%) in the control arm. This imbalance potentially introduced bias in favor of the control C6/P arm for OS, as potentially more death events have been missed in the C6/P arm through early censoring of patients with relatively poor prognosis.
- The open label design of the study meant that the treatment arm to which patients were randomized was known, and this may have affected subsequent therapies patients received. None of the patients in the O/C4/P arm and 6/81 (7.4%) of the patients in the C6/P arm went on to receive a PARP inhibitor, including 5/21 (24%) in the *BRCAm* subgroup.
- There was no significant difference in TSST in the ITT population. However, in patients with a *BRCA* mutation, there was a statistically significant benefit in TSST in

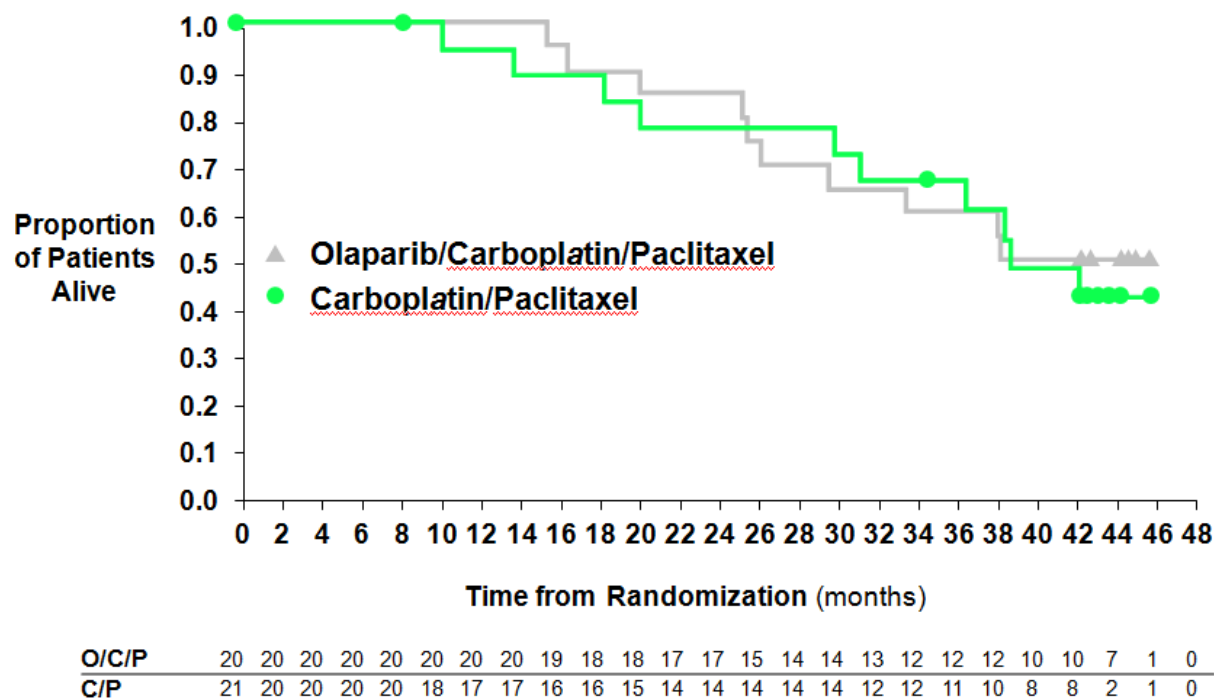
favor of olaparib over placebo (HR: 0.26; 95% CI: 0.11 to 0.59; p=0.0013). These findings provide reassurance that treatment with olaparib maintenance therapy did not adversely affect sensitivity to subsequent chemotherapy.

- In the *BRCAm* group, the overall survival Kaplan-Meier curves cross and median in the olaparib treatment group has not been reached as of the DCO of 31 January 2014 (Figure 13).

Table 16 Overall survival (OS) and time to second subsequent therapy or death (TSST) - Study 41

	ITT		<i>BRCAm</i> patients	
	Olaparib/ carboplatin AUC4/ paclitaxel, followed by olaparib maintenance therapy	Carboplatin AUC4/ paclitaxel, with no maintenance therapy	Olaparib/ carboplatin AUC4/ paclitaxel, followed by olaparib maintenance therapy	Carboplatin AUC4/ paclitaxel, with no maintenance therapy
Overall survival (OS)				
No events: No patients (%)	54:81 (67)	47:81 (58)	10:20 (50)	10:21 (48)
Median time (months)	33.8	37.6	Median not reached	39.2
HR (95% CI)	1.17 (0.79-1.73)		1.28 (0.39-4.18)	
P value (2-sided)	0.4379		0.6861	
Time to second subsequent therapy or death (TSST)				
No events: No patients (%)	60:81 (74)	55:81 (68%)	11:20 (55)	16:21 (76)
Median time (months)	22.1	22.3	39.9	18.1
HR (95% CI)	0.83 (0.57-1.20)		0.26 (0.11-0.59)	
P value (2-sided)	0.3162		0.0013	

Figure 13 Overall survival in *BRCAm* patients - Study 41



OCP= olaparib/carboplatin/paclitaxel (olaparib arm)
C/P=carboplatin/paclitaxel (control arm).

4.2 Study 12

- Study 12 was a randomized, open-label phase II dose-finding study of olaparib monotherapy (200 mg bd and 400 mg bd) vs pegylated liposomal doxorubicin (PLD) in *gBRCAm* ovarian cancer patients who had failed previous platinum therapy and were not considered candidates for further platinum treatment. Consistent with the FDA-approved indication for PLD, patients were substantially pre-treated having received a median of 3 prior lines of therapy.
- Germline *BRCA* mutation status was determined prospectively via local testing and reported in the CRF. Overall, 84% of patients had a *BRCA1* mutation and 16% had a *BRCA2* mutation.
- PLD is a recommended standard treatment for patients with relapsed ovarian cancer. The treatment effect for PLD, is reported to be greater in PSR disease and in *gBRCAm* ovarian cancer patients (PLD USPI 2013; Gordon et al 2001; Safra 2011).
- Key efficacy findings are summarized in Table 17.

Table 17 **Summary of PFS and OS results - Study 12**

	Study 12 ITT (by design all patients were known to be <i>gBRCAm</i>) PFS DCO 15 September 2009 OS DCO 30 April 2010			
	Olaparib 400 mg bd (n=32)	Olaparib 200 mg bd (n=32)	Olaparib 200 mg + 400 mg bd (n=64)	PLD (n=33)
PFS				
No events: No patients (%)	20:32 (63)	19:32 (59)	39:64 (61)	20:33 (61)
Median PFS, months	8.8	6.5	Not calculated	7.1
HR (95% CI)	0.86 (0.45-1.62)	0.91 (0.48-1.74)	0.88 (0.51-1.56)	–
P value	p=0.6316	p=0.7794	p=0.6604	
OS				
No events: No patients (%)	11:31 (35)	9:32 (28)	20:63 (32)	13:33 (39)
Median OS, months	Not reached	Not reached	Not reached	18.3
HR (95% CI)	1.09 (0.47-2.47)	0.67 (0.27-1.57)	0.85 (0.42-1.77)	–
P value	p=0.8435	p=0.3557	p=0.6525	

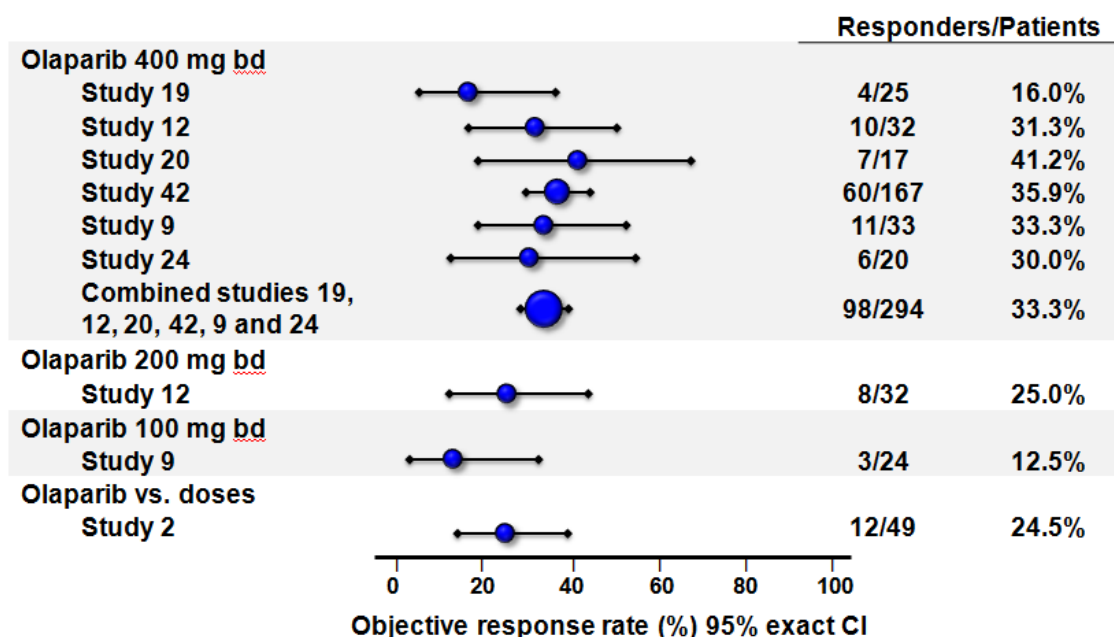
- The primary analysis of PFS compared both doses of olaparib to PLD and did not demonstrate a statistically significant difference between olaparib monotherapy and PLD in patients with *gBRCAm* ovarian cancer.
 - PFS analyses based on independent central review were consistent with the primary analyses of PFS.
 - A subgroup analysis of the platinum-sensitive population was prespecified in the SAP. The HR for PFS was numerically higher (not statistically significant) for olaparib 400 mg bd vs PLD (HR 0.61, 95% CI 0.24-1.50; p=0.29) than for olaparib 200 mg vs PLD (PFS: HR 0.82, 95% CI 0.31-2.02; p=0.68).
- Whilst no patients had a complete response, 8 [25%], 10 [31%] and 6 [18%] patients in the olaparib 200 mg bd, olaparib 400 mg bd and PLD groups, respectively had a best objective response of partial response. The proportion of patients with evidence of refractoriness (ie, a best response of progression) was lowest for the olaparib 400 mg bd group with only 3/32 (9%) patients compared with 8/32 (25%) and 9/33 (27%) for the olaparib 200 mg bd and PLD groups, respectively.
- Once patients on PLD had centrally confirmed objective radiological progression, they were given the opportunity to receive treatment with olaparib (400 mg bd). At the time of the PFS analysis (PFS DCO: 15 September 2009) a total of 14/33 patients had crossed over from the PLD group to the olaparib 400 mg bd group.

- All 14 patients had shown disease progression according to investigator assessment prior to cross-over, hence this did not impact the primary assessment of PFS. In 2/14 patients, crossover to olaparib occurred before centrally confirmed progression, however sensitivity analysis assessing attrition bias using central review data gave consistent results to the main central review PFS result.
- Cross-over is however likely to have impacted the analysis of OS in this study - at the time of the PFS analysis, the protocol was amended so that further OS follow-up would not continue, resulting in the OS analysis being performed on 33 events (DCO 30 April 2010) and not the originally planned 40 death events.

4.3 Cross-study analysis of objective response rate in *BRCA* mutated (*BRCAm*) ovarian cancer patients

- Consistent response rates (ie, complete response or partial response by RECIST 1.0) have been demonstrated with olaparib across the seven supportive efficacy studies referenced in this NDA ([Figure 14](#)).
- Demonstration of tumor shrinkage in the maintenance treatment setting in Study 19 is not possible for those patients entering the study in complete response to platinum-based chemotherapy, however patients in partial response at study entry are assessable for further response.
- Apart from Study 19, response rates at the 400 mg bd monotherapy dose were similar across studies, with a combined response rate of 33% (98 responders out of 294 patients evaluable for response in Studies 19, 12, 20, 42, 09 and 24). This combined response rate is numerically higher than the response rates observed for 200 mg bd and 100 mg bd monotherapy doses.

Figure 14 Objective response rate (%) across all studies of olaparib in *BRCAm* ovarian cancer



Responders are patients having a best objective response of complete response or partial response.

Please note that in all studies shown above except Study 19, *BRCA* mutation status was based on assessment of *gBRCA* mutation status only. Figure presents data for patients with measurable disease at entry.

5. CLINICAL SAFETY

At the time of the safety data cut-off for the NDA submission (20 May 2013), 2034 patients had received treatment with olaparib, either alone or in combination, at doses ranging from 10 mg once daily to 600 mg bd. As of 02 May 2014, this number increased to 2618 patients. Adverse events have been collected for patients on treatment or within 30 days post treatment discontinuation, up to the time of database closure for each study. In addition, study investigators were required to report any SAEs for patients who continue on treatment beyond end of study, and to report any SAEs that they consider to be possibly related to investigational product even after treatment discontinuation. The first subject was enrolled in 2005 and the most recent studies started recruiting patients in 2014.

Across the clinical program, the 400 mg bd dose of olaparib has demonstrated a consistent and well-defined tolerability profile suitable for use as a long-term maintenance therapy. Evaluation of olaparib safety for the proposed indication is based on the 264 patients enrolled and treated in the pivotal Study 19 (olaparib 400 mg bd maintenance therapy n=136; matching placebo n=128), supported by a large supportive pooled dataset of 735 patients with advanced solid tumors who were treated with 400 mg bd olaparib capsules as a monotherapy from 11 studies in the clinical trial program (including Study 19).

The majority of patients in the pooled dataset (508/735) had ovarian cancer. Patients with other advanced solid tumors, including breast (n=140), colorectal (n=37), pancreas (n=24) or prostate (n=8) cancers were also treated in these studies and included in the pool. With the exception of Study 19, where olaparib was administered in the maintenance setting to responding patients, the treatment setting was as a late line of therapy to patients with relapsed, progressive disease. AE information was collected for patients on treatment or within 30 days of completing treatment, up to the time of study closure. As a consequence, comparisons of subgroups within the monotherapy pooled dataset must be interpreted with caution, as apparent imbalances may be affected by differences in the patient populations and diseases under study and treatment duration up to study closure. Pooled safety data are considered supplementary to the presentation of data from Study 19.

The 735 patients in the pooled safety dataset includes 397 ovarian cancer patients who had a *BRCA* mutation detected by blood or tumor testing, the majority (376) of whom had a *gBRCA* mutation. Of note, an additional 66 patients received olaparib 400 mg bd in the maintenance phase of Study 41. These 66 patients are not included in the pooled dataset as they had also received olaparib in combination with carboplatin and paclitaxel.

Key baseline characteristics for the studies contributing the majority (80%) of patients to the 400 mg bd monotherapy pooled data set are presented in [Table 18](#).

Table 18 Key baseline characteristics by study: patients randomized to olaparib 400mg bd

Study	Study 19	Study 12	Study 08	Study 09	Study 20	Study 42
N (all patients)	136	32	27	33	64	298
N of US patients	23	10	14	18	0	63
N (<i>gBRCA</i> m)	53	32	27	33	17	298
Median age, years (range)	58 (21–89)	54 (35–76)	44 (32–72)	54 (35–74)	58 (39–84)	56 (29–79)
Race (% White)	96	100	96.3	93.9	90.6	95.0
ECOG PS (%)						
0/1	98	100	93	100	92	93
2	1	0	7	0	6	6
Unknown	2	0	0	0	2	<1
Median number of prior chemotherapy regimens (range)	3 (2–11)	3 (1–6)	3 (1–5)	3 (1–10)	3 (1–10)	4 (1–14)

The exposure of patients in the 400mg bd monotherapy pooled dataset to olaparib, at the time of the NDA data cut-off of 20 May 2013 is summarised in [Table 19](#). The median treatment

duration was 5.5 months and 6.5 months for all patients and patients with *BRCAm* ovarian cancer, respectively.

Table 19 **Number (%) of patients on treatment: 400 mg bd monotherapy pooled dataset (Safety Analysis)**

Treatment duration^a	All patients (advanced solid tumors) N=735	<i>BRCAm</i> patients (N=397)^b
≥6 months	320 (43.5)	207 (52.1)
≥12 months	140 (19.0)	94 (23.7)
≥24 months	41 (5.6)	25 (6.3)
≥36 months	19 (2.6)	13 (3.3)

Data are included from each study up to the time of clinical database closure.

a Rows are cumulative.

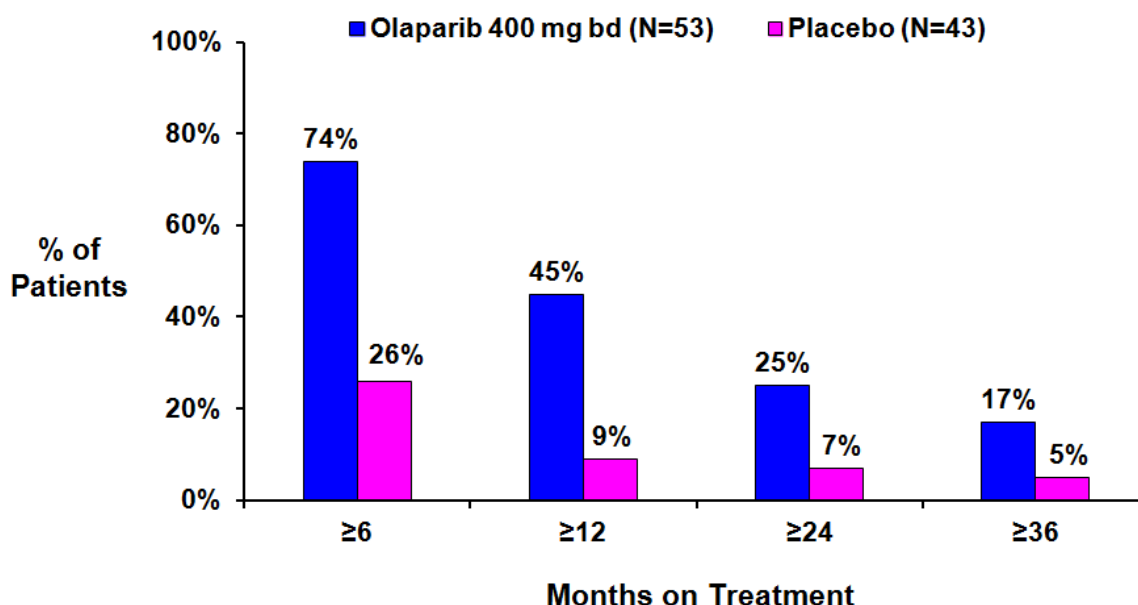
b *BRCA* mutation status determined by blood and/or tumor testing.

5.1 Exposure and tolerability in Study 19

At the time of the data cut-off in Study 19, median follow-up was 37.3 months (just over 3 years). The median duration on olaparib maintenance therapy was 8.7 months for the Safety Analysis population and 11.1 months for patients with a *gBRCA* mutation, compared to 4.6 months for the Safety Analysis population and 4.4 months for the *gBRCA* placebo groups.

The number of patients remaining on study treatment at 1-year, 2-years and 3-years after randomization, was at least greater than three times higher in the olaparib group compared with patients assigned to placebo (40% vs 11%, 24% vs 4% and 14% vs 2%) in the ITT population. A similar observation was made for patients with a *gBRCA* mutation, as shown in [Figure 15](#).

Figure 15 Duration of treatment in patients with *gBRCA* mutation - Study 19



At data cut-off for the Safety Analysis, 23/136 (17%) patients remained on olaparib maintenance treatment and 3/129 (2%) patients remained on placebo. Most patients who had discontinued study treatment did so as the result of ovarian cancer progression (87/113 [77%] olaparib, 110/125 [88%] placebo), and AEs leading to discontinuation were infrequent (see Section 5.2.3). Findings were consistent in the *gBRCAm* subgroup.

Dose interruptions and reductions were permitted in the protocol to manage adverse events (AEs). In the olaparib arm, a total of 34.6% of patients in the olaparib arm (9.4% placebo) had an AE leading to dose interruption and 20.6% of patients in the olaparib arm (2.3% placebo) had an AE leading to dose reduction (Table 37 in the appendices). Despite these dose modifications, the majority (ranging from 67% to 81% across time periods) of patients received between 600 and 800 mg mean daily dose of olaparib throughout the study (Table 20). The median number of days during which the full intended dose of olaparib (400 mg bd) was received was 170 days (approximately 5.6 months) and 208 days (~6.8 months) in patients with a *gBRCA* mutation.

Table 20 Mean daily dose of olaparib by time period - Study 19 (Safety Analysis)

Olaparib mean daily dose (mg)	Number (%) patients by time period				
	Up to 3 months (n=136)	>3 to ≤ 6 months (n=116)	>6 to ≤ 9 months (n=86)	>9 to ≤ 12 months (n=67)	> 12 months (n=54)
≤ 200	2 (2)	7 (6)	9 (11)	6 (9)	4 (7)
>200 to ≤ 400	10 (7)	22 (19)	17 (20)	16 (24)	10 (19)

Table 20 Mean daily dose of olaparib by time period - Study 19 (Safety Analysis)

Olaparib mean daily dose (mg)	Number (%) patients by time period				
	Up to 3 months (n=136)	>3 to ≤6 months (n=116)	>6 to ≤9 months (n=86)	>9 to ≤12 months (n=67)	> 12 months (n=54)
>400 to ≤600	14 (10)	4 (3)	2 (2)	0	0
>600 to ≤800	110 (81)	83 (72)	58 (67)	45 (67)	40 (74)

5.2 Adverse events

An overview of safety in Study 19 is provided in [Table 21](#).

During the maintenance treatment period, patients treated with olaparib experienced more AEs of grade ≥3 (40.4 % vs 21.9%), more serious AEs (SAEs; 18.4% vs 8.6%) and more AEs leading to discontinuation of treatment (5.1% vs 1.6%) compared with placebo-treated patients. Findings were consistent with the *gBRCAm* subgroup in Study 19, and in the 400 mg monotherapy pool (see [Table 40](#) in the appendices).

Adverse events were reported throughout the dosing period:

- 96% (131/136) of patients treated with olaparib reported the onset of one or more AEs during the first 3 months of treatment, compared with 114/128 (89%) on placebo.
- 66% (85/128) of patients reported the onset of one or more AEs between 3 and 6 months of treatment, compared with 69/119 (58%) on placebo.
- 59% (36/61) of patients reported the onset of one or more AEs between 12 and 15 months of treatment, compared with 9/16 (56%) on placebo.
- 25% (8/32) of patients reported the onset of one or more AEs between 24-27 months of treatment, compared with 1/6 (17%) on placebo.

Table 21 Number (%) of patients who had at least one AE in any category – Study 19

AE category	Safety Analysis		<i>gBRCAm</i> patients	
	Number (%) patients		Number (%) patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Any AE	132 (97.1)	119 (93.0)	52 (98.1)	41 (95.3)
Any AE of grade 3 or higher	55 (40.4)	28 (21.9)	17 (32.1)	8 (18.6)
Any AE with outcome = death	2 (1.5)	0	1 (1.9)	0

Table 21 **Number (%) of patients who had at least one AE in any category – Study 19**

AE category	Safety Analysis		<i>gBRCAm</i> patients	
	Number (%) patients		Number (%) patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Any SAE	25 (18.4)	11 (8.6)	11 (20.8)	3 (7.0)
Any AE leading to discontinuation of study treatment	7 (5.1)	2 (1.6)	5 (9.4)	0

5.2.1 Most common AEs by preferred term (any severity) and grade ≥ 3

The most frequently occurring AEs reported with olaparib in Study 19 included nausea, fatigue, vomiting, diarrhea, abdominal pain and anemia (Table 22). These common AEs were generally intermittent, low grade (CTCAE grade 1 or 2) and did not generally require dose modification or lead to discontinuation of study treatment. Findings were consistent with the *gBRCAm* subgroup in Study 19, and across the larger 400 mg monotherapy pooled dataset (see Table 41 in the appendices).

A higher percentage of all patients in the olaparib group reported AEs of grade ≥ 3 (40.4%) compared with the placebo group (21.9%) (Table 23). The difference in CTCAE Grade 3 AEs is apparent in the first 3 months of treatment with olaparib, and is not explained by the longer duration of exposure on the olaparib arm (Figure 16). The reporting rate for individual events was low, with the most common AEs of grade ≥ 3 reported on olaparib treatment being fatigue (7.4% of all patients) and anemia (5.1% of all patients). Findings were consistent with the *gBRCAm* subgroup in Study 19, and across the larger 400 mg monotherapy pooled dataset (see Table 23 in the appendices). In the *gBRCAm* group, approximately 50% of the events had an onset within the first 60 days. At the time of the DCO, 70% of the events had resolved. In approximately 60% of cases this followed a dose modification, and in 40% no action was taken. Only three events had an onset date beyond 12 months after starting treatment with olaparib.

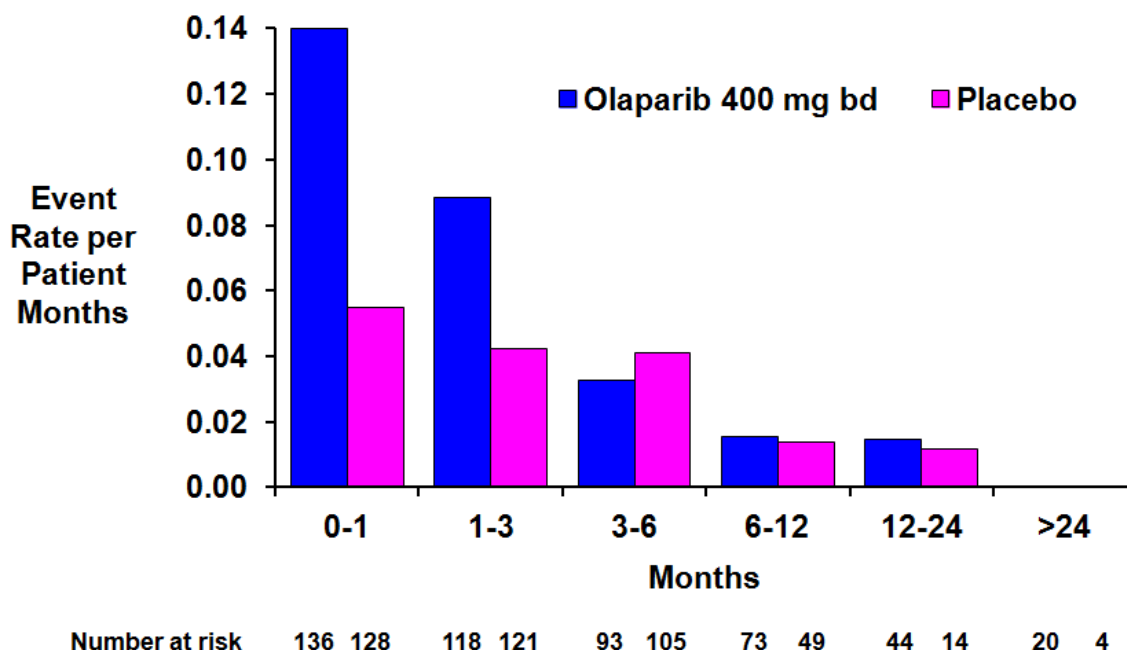
Table 22 **Number (%) of patients with most common AEs (≥20% in the Safety Analysis) – Study 19**

Preferred term	Safety Analysis				<i>gBRCAm</i> patients			
	Any grade		Grade ≥3		Any grade		Grade ≥3	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43	Olaparib 400 mg bd N=136	Placebo N=128
Nausea	96 (70.6)	46 (35.9)	3 (2.2)	0	40 (75.5)	16 (37.2)	1 (1.9)	0
Fatigue	71 (52.2)	50 (39.1)	10 (7.4)	4 (3.1)	28 (52.8)	18 (41.9)	2 (3.8)	1 (2.3)
Vomiting	46 (33.8)	18 (14.1)	3 (2.2)	1 (0.8)	17 (32.1)	4 (9.3)	2 (3.8)	0
Diarrhea	37 (27.2)	31 (24.2)	3 (2.2)	3 (2.3)	15 (28.3)	9 (20.9)	2 (3.8)	1 (2.3)
Abdominal pain	34 (25.0)	34 (26.6)	3 (2.2)	4 (3.1)	12 (22.6)	15 (34.9)	0	1 (2.3)
Abdominal pain upper	24 (17.6)	10 (7.8)	0	1 (0.8)	13 (24.5)	3 (7.0)	0	0
Anemia	29 (21.3)	7 (5.5)	7 (5.1)	1 (0.8)	13 (24.5)	2 (4.7)	2 (3.8)	1 (2.3)
Constipation	28 (20.6)	14 (10.9)	0	0	9 (17.0)	4 (9.3)	0	0
Decreased appetite	28 (20.6)	17 (13.3)	0	0	13 (24.5)	6 (14.0)	0	0
Headache	28 (20.6)	16 (12.5)	0	1 (0.8)	12 (22.6)	7 (16.3)	0	1 (2.3)

Table 23 **Number (%) of patients with the most common AEs of grade 3 or higher in Study 19, Safety Analysis**

System organ class/ Preferred term	Safety Analysis		<i>gBRCAm</i> patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Any AE of \geq grade 3	55 (40.4)	28 (21.9)	17 (32.1)	8 (18.6)
Blood and lymphatic disorders	12 (8.8)	3 (2.3)	4 (7.5)	1 (2.3)
Anemia	7 (5.1)	1 (0.8)	2 (3.8)	1 (2.3)
Leukopenia	3 (2.2)	0	2 (3.8)	0
Neutropenia	5 (3.7)	1 (0.8)	3 (5.7)	0
Gastrointestinal disorders	12 (8.8)	10 (7.8)	3 (5.7)	2 (4.7)
Abdominal pain	3 (2.2)	4 (3.1)	0	1 (2.3)
Diarrhea	3 (2.2)	3 (2.3)	2 (3.8)	1 (2.3)
Nausea	3 (2.2)	0	1 (1.9)	0
Small intestinal obstruction	2 (1.5)	3 (2.3)	0	1 (2.3)
Vomiting	3 (2.2)	1 (0.8)	2 (3.8)	0
General disorders and administration site conditions	13 (9.6)	4 (3.1)	4 (7.5)	1 (2.3)
Fatigue	10 (7.4)	4 (3.1)	2 (3.8)	1 (2.3)
Musculoskeletal and connective tissue disorders	8 (5.9)	0	5 (9.4)	0
Back pain	3 (2.2)	0	2 (3.8)	0
Investigations	8 (5.9)	5 (3.9)	1 (1.9)	1 (2.3)
Hemoglobin decreased	2 (1.5)	0	0	0
Respiratory, thoracic and mediastinal disorders	3 (2.2)	0	2 (3.8)	0
Dyspnea	2 (1.5)	0	1 (1.9)	0

Figure 16 Life table plot for time to first grade ≥ 3 adverse event



5.2.2 Serious adverse events (SAEs)

There was a higher proportion of SAEs reported in the olaparib arm compared with placebo (18.4% vs 8.6% in the Safety Analysis, and 20.8% vs 7.0% in the subgroups of patients with *gBRCA* mutation). The difference in incidence of SAEs may be partly explained by the longer duration of exposure on the olaparib arm (Figure 17). The only SAEs reported in >1 patient in either treatment group were: anemia (3 patients on olaparib), small intestinal obstruction (2 patients on olaparib, 3 patients on placebo), dyspnea (2 patients on olaparib) and gastritis (2 patients on placebo). There was no clear pattern of events associated with this difference between treatment arms, and in the *gBRCA* subgroup, no individual SAE preferred term was reported in >1 patient. At the time of the DCO, 11 patients in the *gBRCA* group had reported 20 SAEs, of which 17 had resolved. Eleven required a dose modification (9 temporary interruptions and 2 dose reductions), 2 had not resolved and one was an AE leading to death (hemorrhagic stroke). SAEs for Study 19 are summarized in Table 43 in the appendices and at the MedDRA System Organ Class (SOC) level in Table 24 below. The highest frequency of reported SAEs were ‘blood and lymphatic system disorders’ and ‘gastrointestinal disorders’.

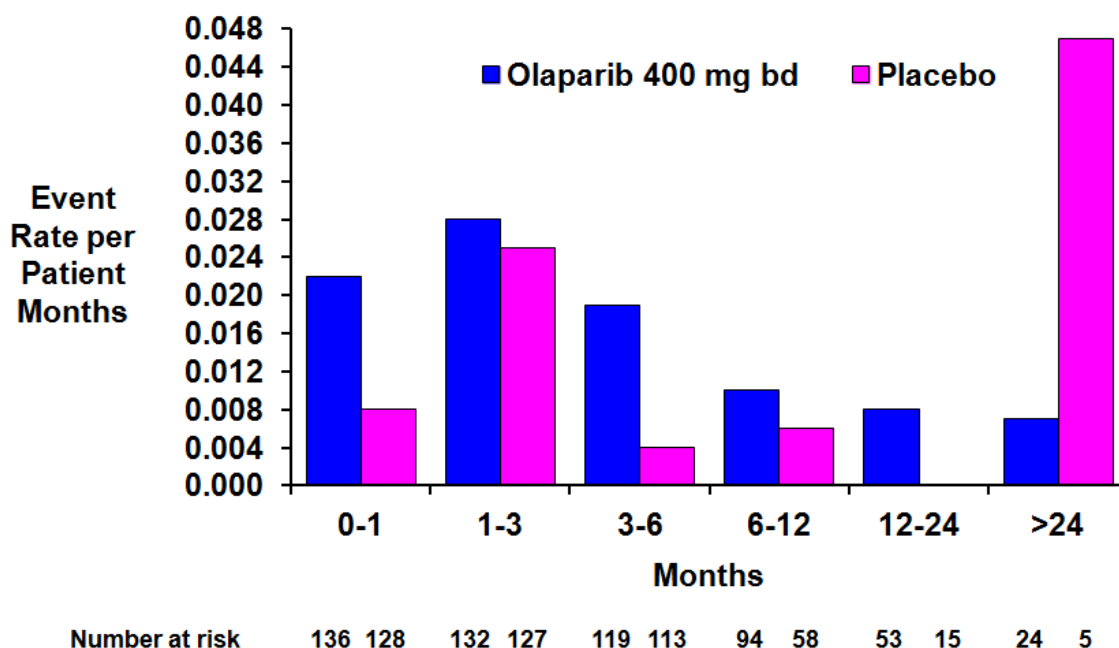
Table 24 Number (%) of patients reporting SAEs by SOC - Study 19

System organ class	Safety Analysis		<i>gBRCA</i> patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Any SAE	25 (18.4)	11 (8.6)	11 (20.8)	3 (7.0)

Table 24 **Number (%) of patients reporting SAEs by SOC - Study 19**

System organ class	Safety Analysis		<i>gBRCAm</i> patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Blood and lymphatic system disorders	5 (3.7)	0	1 (1.9)	0
Cardiac disorders	1 (0.7)	0	1 (1.9)	0
Gastrointestinal disorders	7 (5.1)	7 (5.5)	2 (3.8)	2 (4.7)
General disorders & administration site conditions	2 (1.5)	0	2 (3.8)	0
Hepatobiliary disorders	1 (0.7)	0	0	0
Immune system disorders	1 (0.7)	0	0	0
Infections and infestations	4 (2.9)	3 (2.3)	4 (7.5)	2 (4.7)
Injury, poisoning and procedural complications	2 (1.5)	0	1 (1.9)	0
Metabolism and nutrition disorders	0	1 (0.8)	0	1 (2.3)
Musculoskeletal and connective tissue disorders	1 (0.7)	0	1 (1.9)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7)	1 (0.8)	0	0
Nervous system disorders	2 (1.5)	0	1 (1.9)	0
Respiratory, thoracic and mediastinal disorders	4 (2.9)	0	3 (5.7)	0
Vascular disorders	1 (0.7)	1 (0.8)	1 (1.9)	0

Figure 17 Life table plot for time to first SAE – Safety Analysis



A higher proportion (25.2%) of patients in the 400 mg bd monotherapy pool reported SAEs compared with patients who received olaparib in Study 19 (18.4%) (see [Table 44](#) in the appendices). Similarly, a higher proportion (27.7%) of patients in the *BRCAm* subgroup in the monotherapy pool reported SAEs compared with patients who received olaparib in the *gBRCAm* subgroup in Study 19 (20.8%). This difference may reflect the more advanced stage of disease of patients in the pool compared with Study 19.

Consistent with Study 19, the most common SOC reported for SAEs reported by patients in the 400 mg bd monotherapy pool were blood and lymphatic disorders (most commonly reported preferred term anemia, 2.9% patients) and gastrointestinal disorders (intestinal obstruction, small intestinal obstruction, vomiting, abdominal pain; 1.6% to 1.9% of patients).

5.2.3 Adverse events leading to discontinuation of study drug

Adverse events leading to discontinuation occurred infrequently (see [Table 38](#) in the appendices).

- In the Safety Analysis, 5.1% (7/136) of the patients who received olaparib had AEs leading to discontinuation, compared with 2/128 (1.6%) patients in the placebo arm.
- In the *gBRCAm* subgroup, 9.4% (5/53) of the patients who received olaparib had AEs leading to permanent discontinuation (none in the placebo arm).

In the Safety Analysis, no single event leading to discontinuation was reported in >1 patient in either treatment group. In the olaparib arm, 7 patients had 9 separate events reported, 5 of which resolved with permanent treatment discontinuation; 2 resulted in death (cholestatic jaundice related to disease progression and hemorrhagic stroke) and 2 were still present at the DCO 26 November 2012: myalgia (reported 3 years before DCO) and thrombocytopenia (reported 1 month before DCO). Time from start of treatment to onset of event ranged from 1 to 1064 days, and three events (cholestatic jaundice, small intestinal obstruction and hemorrhagic stroke) were SAEs.

AEs leading to discontinuation of study treatment were similarly uncommon in the olaparib 400 mg monotherapy pool, and were reported for 43/735 (5.9%) of all patients, including 23/397 (5.8%) of patients with *BRCA* mutation (see [Table 39](#) in the appendices).

5.2.4 Deaths in olaparib treated patients

Of the 816 patients treated with olaparib in Study 19, Study 41 and the 400 mg bd monotherapy pooled dataset, 378 (46.3%) have died. Of these, 346 (91.5%) deaths were attributed solely to the underlying ovarian cancer ([Table 25](#)).

In total, 32/378 (8.4%) olaparib-treated patients died due to adverse events or ‘other’ reasons: 9 patients in Study 19, 7 patients in Study 41 and 16 patients in studies other than Study 19 in the monotherapy pooled dataset (9 of whom came from Study 42, an open-label, non-comparative study to assess the efficacy of olaparib in patients with advanced cancers with a confirmed *gBRCA* mutation). Due to the small numbers of events, all of the deaths are discussed together. Equivalent data are presented for the (*g*)*BRCAm* subgroups in [Table 26](#).

Table 25 Number (%) of patients who died in Study 19, Study 41 and the monotherapy pooled dataset (Safety Analysis)

Category	Study 19		Study 41		monotherapy pool N=735
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib/ carboplatin AUC4/ paclitaxel, followed by maintenance N=81	Carboplatin AUC4/ paclitaxel, no maintenance N=81	
Total number of deaths^a	77 (56.6)	77 (60.2)	54 (66.7)	42 (56.0)	324 (44.1)
Death related to disease under investigation only	68 (88.3)	71 (92.2)	47 (87)	38 (90.4)	299 (92.3)
AE with outcome = death only	1 (1.3)	0	2 (3.7)	0	6 (1.9)
Death related to disease and an AE with outcome = death	2 (2.6)	0	0	0	10 (3.1)

Table 25 Number (%) of patients who died in Study 19, Study 41 and the monotherapy pooled dataset (Safety Analysis)

Category	Study 19		Study 41		monotherapy pool N=735
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib/ carboplatin AUC4/ paclitaxel, followed by maintenance N=81	Carboplatin AUC4/ paclitaxel, no maintenance N=81	
Other deaths	6 (7.8)	6 (7.8)	2 (3.7)	1 (2.4)	9 (2.8)
Unknown	0	0	3 (5.6)	3 (7.1)	0

Data are presented for any deaths that occurred during treatment, during the 30-day follow-up period or after the 30-day follow-up period are presented. Survival status was unknown where patients were censored due to withdrawal of consent or the patient being lost to follow-up.

Table 26 Number (%) of patients who died in Study 19, Study 41 and monotherapy pool: patients with a *BRCA* mutation

Category	Study 19 (<i>gBRCAm</i>) ^a		Study 41 (<i>BRCAm</i>) ^b		Monotherapy pool (<i>BRCAm</i> ovarian cancer) N= 397 ^c
	Olaparib 400 mg bd N=53	Placebo N=43	OC6P N=20	C4P N=21	
Total number of deaths	27 (50.9)	22 (51.2)	54 (66.7)	42 (56.0)	172 (43.3)
Death related to disease under investigation only	22 (81.5)	19 (86.4)	47 (58.0)	38 (50.7)	154 (89.5)
AE with outcome = death only	1 (4.5)	0	2 (2.5)	0	5 (2.9)
Death related to disease and an AE with outcome = death	0	0	0	0	6 (3.5)
Other deaths	4 (14.9)	3 (13.6)	2 (2.5)	1 (1.3)	7 (4.1)
Unknown	0	0	3 (3.7)	3 (4.0)	0

Data are presented for any deaths that occurred during treatment, during the 30-day follow-up period or after the 30-day follow-up. Survival status was unknown where patients were censored due to withdrawal of consent or the patient being lost to follow-up. DCO 31 January 2014.

a Data presented for the 96 *gBRCAm* patients in Study 19. DCO 26 November 2012.

b Data presented for all *BRCAm* patients in Study 41 (as most had mutation status detected from tumor rather than blood).

c *BRCA* mutation status determined by blood and/or tumor testing (includes 21 patients with *BRCA* status from tumor only).

Details of the 32 deaths in olaparib treated patients (other than those reported as due to disease under investigation only) are summarized in Table 47 in the appendices. The most common AEs leading to death were MDS/AML (6 cases) and sepsis (5 cases). Most causes of death

assigned to the ‘other’ category are AEs reported outside of the 30 day follow-up period after study treatment discontinuation.

Deaths in Study 19

Nine deaths were recorded (excluding deaths related to disease under investigation only), of which 2 (hemorrhagic stroke and MDS) were considered to be related to study treatment.

- One patient had the reason for death recorded as AE only:
 - Patient E1808004 (*gBRCA* mutation) died as a result of hemorrhagic stroke during the 30-day follow-up period
- Two patients had the reason for death recorded as disease under study and AE:
 - Patient E0805001 (unknown *gBRCA* mutation status) died in the post-follow-up period on Day 1062 (48 days after stopping treatment) due to progressive ovarian cancer; this patient also had cholestatic jaundice that was considered by the investigator to be the secondary cause of death, and not related to study treatment.
 - Patient E1801002 (*gBRCA* wildtype) died in the post-follow-up period on Day 430 (117 days after stopping treatment) due to progressive ovarian cancer; this patient also had MDS that was considered by the investigator to be the secondary cause of death.
- Six patients had deaths in the category “other” (E0103005, E0302002, E1002002, E1403004, E1505001, E1806001). The ‘other’ causes of death were euthanasia, septic shock, cerebrovascular disorder, cerebral hemorrhage and cause unknown (n=2); all occurred many months after olaparib treatment had been discontinued, and after patients had received subsequent anti-cancer therapy.

Deaths in Study 41

Seven deaths were recorded (excluding deaths related to disease under investigation only), of which 2 (disseminated intravascular coagulation and MDS) were considered to be causally related to olaparib.

- Two patients had the reason for death recorded as AE only:
 - Patient E1405004 died from disseminated intravascular coagulation (related to MDS/AML) after the end of the follow-up period.
 - Patient E1503001 died from MDS.
- Two patients had reason for death ‘other’ (2 sepsis and cardiac infarction) and 3 were ‘unknown’ cause.

Deaths in the pooled monotherapy dataset

Sixteen deaths recorded (excluding deaths related to disease under investigation only, and excluding the 9 patients from Study 19 already discussed) of which 2 (sepsis and MDS) were considered to be causally related to olaparib.

- Thirteen patients of 735 patients had ‘AE with outcome of death only’ (5 patients) or ‘death related to disease and an AE with outcome of death’ (8 patients) reported: sepsis (3), acute leukemia (2), MDS (1), hydronephrosis and pleural effusion (1 each, both in the same patient), intestinal perforation, chronic respiratory failure, pulmonary embolism, chronic obstructive pulmonary disease, suture rupture and cerebrovascular accident (1 each).
- Three patients had the reason for death recorded as ‘other’, the reported terms were: AML, disease progression, and ‘unknown’ cause.

5.2.5 Characterization of the most common adverse events

5.2.5.1 Anemia

Anemia (and decreased hemoglobin) was the most common hematological toxicity reported with olaparib. To allow a comprehensive assessment under the “anemia” term below, AstraZeneca grouped MedDRA preferred terms of anemia, anemia macrocytic, reticulocytosis, hemoglobin decreased, red blood cell count, together with hemoglobin levels from laboratory safety data for the Safety Analysis of all patients in Study 19.

A summary of anemia clinical AEs and laboratory changes is provided in [Table 27](#).

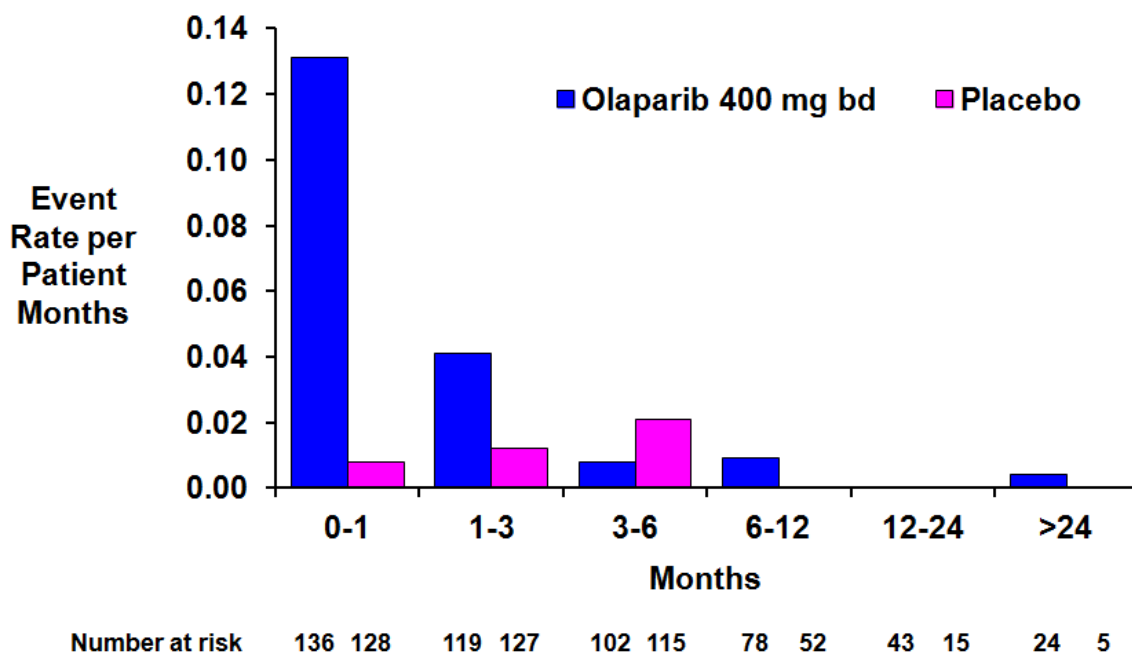
Table 27 **Number (%) of patients who had at least one AE of anaemia (grouped PTs) reported in any category: Study 19, Safety Analysis**

AE category ^a	All patients	
	Olaparib 400 mg bd N=136	Placebo N=128
Anaemia (including anaemia, anaemia macrocytic, reticulocytosis, haemoglobin decreased, red blood cell count decreased)		
Any AE	32 (23.5)	9 (7.0)
AE of Grade 3 or higher	9 (6.6)	1 (0.8)
AE with outcome = death	0	0
SAE	3 (2.2)	0
AE leading to discontinuation of study treatment	0	0
AE leading to temporary interruption of study treatment	5 (3.7)	0
AE leading to dose reduction of study treatment	4 (2.9)	1 (0.8)

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

- Study 19 required patients to have a hemoglobin level of ≥ 9.0 g/dL for eligibility. In total, 34/265 (12.8%) patients reported anemia at study entry, with 8.8% of patients on olaparib and 7.8% on placebo having grade 2 laboratory hemoglobin values at baseline.
- In Study 19, overall 14/136 patients on olaparib (10.3%) compared to 1/128 patients on placebo (0.8%) received one or more transfusions during the study. All of these patients had grade ≥ 2 decrease in hemoglobin.
- A review of the patients requiring blood transfusions in Study 19 has demonstrated that 7/14 of the olaparib treated patients received one transfusion, 6 patients received a transfusion on two occasions, and one patient received a transfusion on three occasions. Details are provided in [Table 45](#) in the appendices. The placebo-treated patient received four transfusions. Ten of the patients who received a transfusion during treatment continued on olaparib for a median of 182 days (94 to 566 days) or years after the first transfusion. Four patients discontinued within 8 days after the first transfusion; in all but one case this was due to disease progression. One patient (E1808004) discontinued due to pancytopenia and later reported an SAE of MDS.
- Anemia was rarely associated with dose interruptions and dose reductions of olaparib: 3.7% and 2.9% of all patients in Study 19, respectively:
 - Anemia is a common AE routinely managed by physicians treating patients with ovarian cancer. Grade 2 reflects a hemoglobin level of <100 to 80 g/L, with grade 3 values between 65 to 80 g/L. Clinically, dependent on individual patient circumstances, it is considered that some patients may require treatment for anemia within the grade 2 criteria. When clinically indicated, blood transfusions may be required to treat patients developing anemia on olaparib treatment. Dose interruptions and dose reductions can also be utilized in the management of patients developing anemia on olaparib therapy.
 - Baseline hematological testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of olaparib treatment and periodically after this time to monitor for clinically significant changes in any parameter during treatment.

Figure 18 Life plot table of time to first onset of anemia (grouped term)



5.2.5.2 Nausea and vomiting

A summary of nausea and vomiting clinical AEs is provided in [Table 28](#).

Table 28 Number (%) of patients who had at least one AE of nausea or vomiting reported in any category: Study 19, Safety Analysis

AE category ^a	All patients	
	Olaparib 400 mg bd N=136	Placebo N=128
Nausea		
Any AE	96 (70.6)	46 (35.9)
AE of CTCAE Grade 3 or higher	3 (2.2)	0
AE with outcome = death	0	0
SAE	0	0
AE leading to discontinuation of study treatment	1 (0.7)	1 (0.8)
AE leading to temporary interruption of study treatment	7 (5.1)	1 (0.8)
AE leading to dose reduction of study treatment	5 (3.7)	0
Vomiting		

Table 28 **Number (%) of patients who had at least one AE of nausea or vomiting reported in any category: Study 19, Safety Analysis**

AE category ^a	All patients	
	Olaparib 400 mg bd N=136	Placebo N=128
Any AE	46 (33.8)	18 (14.1)
AE of CTCAE Grade 3 or higher	3 (2.2)	1 (0.8)
AE with outcome = death	0	0
SAE	1 (0.7)	0
AE leading to discontinuation of study treatment	0	0
AE leading to temporary interruption of study treatment	11 (8.1)	1 (0.8)
AE leading to dose reduction of study treatment	4 (2.9)	1 (0.8)

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

^b As assessed by the investigator.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

- The reported incidences of nausea and vomiting, of any grade and of grade >3, was approximately twice as high for olaparib vs placebo (nausea: 70.6% vs 35.9% and 2.2% vs 0%; vomiting: 33.8% vs 14.1% and 2.2% vs 0.8% for olaparib and placebo, respectively). The majority of cases were reported as intermittent and low grade (grade 1 or 2), and only infrequently led to permanent discontinuation of treatment (2 patients, 1 in each arm, discontinued treatment due to nausea).
- Dose reduction and interruptions were utilized in a small number of patients to manage the events of nausea and vomiting in Study 19, with 5.1% nausea leading to a temporary dose interruption (8.1% vomiting) and 3.7% required a dose reduction of olaparib treatment for nausea (2.9% vomiting)
- Treatment for nausea was received by 50.0% patients in the olaparib arm and in 17.4% patients in the placebo arm, and treatment for vomiting was received by 30.4% olaparib treated patients and 16.7% of placebo treated patients
- Nausea and vomiting are routinely managed by oncologists treating ovarian cancer. The low grade, intermittent and non-cumulative nature of the events occurring on olaparib treatment mean that nausea and vomiting can be effectively treated empirically using standard anti-emetic treatment and prophylaxis is not required. Temporary dose interruptions or dose reductions of olaparib may be required in a small number of patients.

Figure 19 Life plot table of time to first onset of nausea

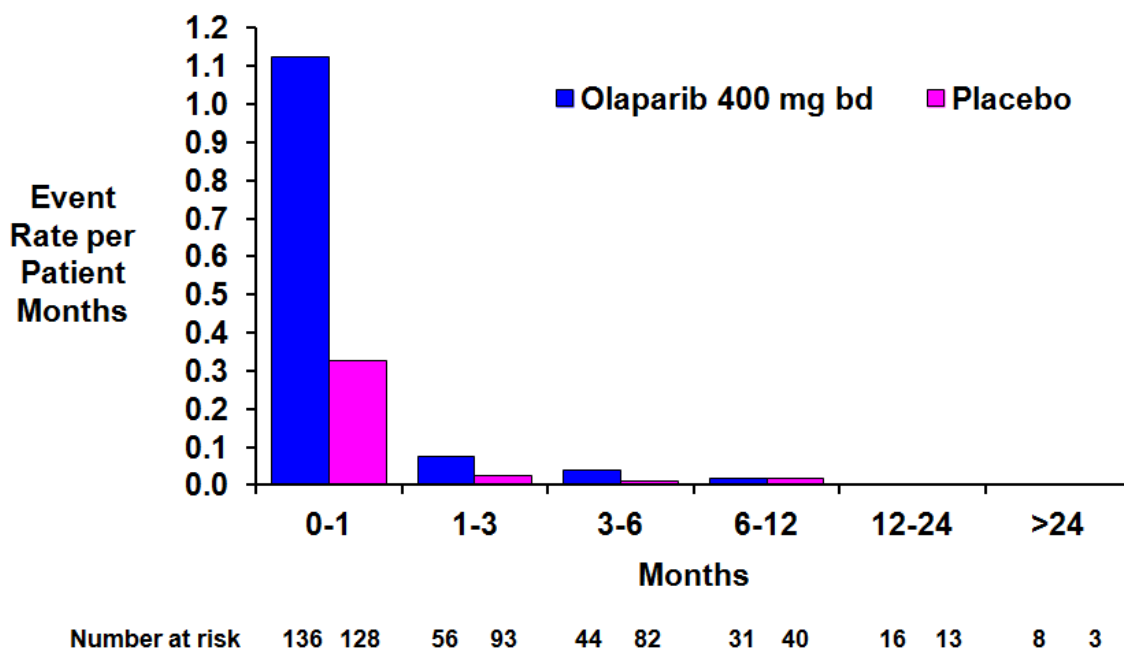
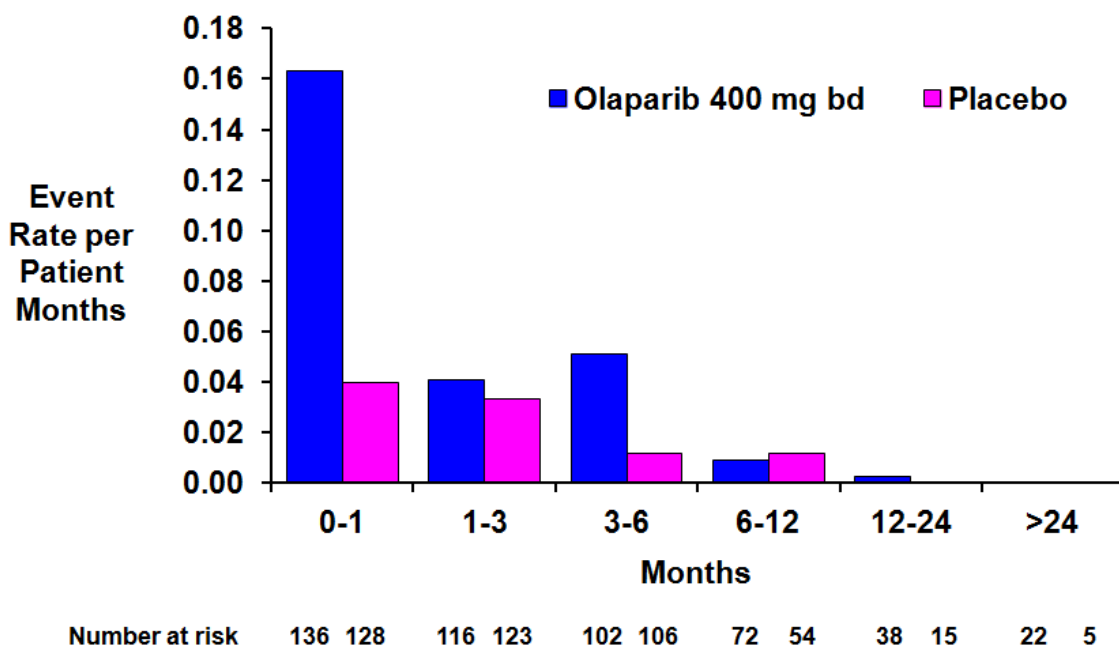


Figure 20 Life plot table of time to first onset of vomiting



5.2.5.3 Fatigue/asthenia

A summary of fatigue/asthenia clinical AEs is provided in [Table 29](#).

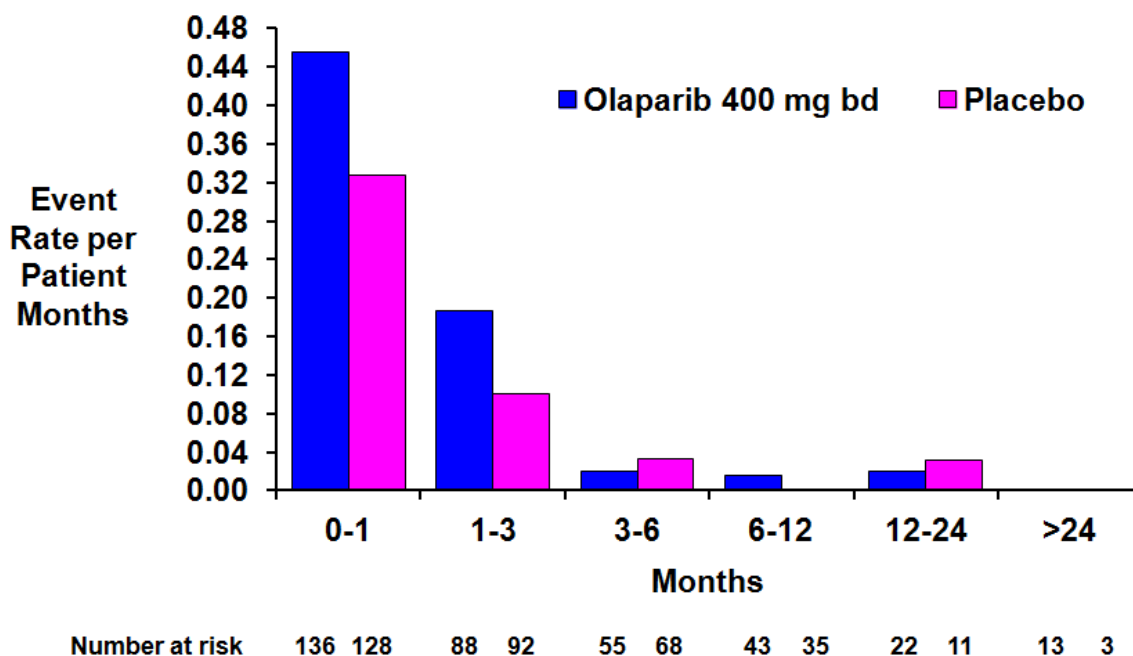
Table 29 **Number (%) of patients who had at least one AE of fatigue or asthenia reported in any category: Study 19, Safety Analysis**

AE category ^a	All patients	
	Olaparib 400 mg bd N=136	Placebo N=128
Any AE	84 (61.8)	59 (46.1)
AE of CTCAE Grade 3 or higher	11 (8.1)	4 (3.1)
AE with outcome = death	0	0
SAE	0	0
AE leading to discontinuation of study treatment	0	0
AE leading to temporary interruption of study treatment	8 (5.9)	2 (1.6)
AE leading to dose reduction of study treatment	8 (5.9)	0

^a Patients with multiple events reported in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

The reported incidences of fatigue/asthenia, of any grade (61.8% vs 46.1%) and of grade ≥ 3 (8.1% vs 3.1%), was higher for olaparib vs placebo, respectively. The majority of cases were reported low grade (grade 1 or 2) and in no case did an event of fatigue/asthenia lead to permanent discontinuation of olaparib. The onset of fatigue/asthenia was early, with most patients reporting an event in the first three months ([Figure 21](#)).

Figure 21 Life plot table of time to first onset of fatigue/asthenia



5.2.5.4 Adverse events of special interest

Secondary MDS/AML

Development of secondary myelodysplastic syndrome (MDS)/therapy-related acute myeloid leukemia (AML) is an AE of interest, as it may be related to products that affect DNA repair mechanisms.

At the time of submission of the NDA, 16 of the 2034 patients who had received olaparib reported an event of MDS and/or AML, giving a cumulative reporting rate of 0.78%. As of 02 May 2014, an additional 5 reports have been received, giving a total of 21/2618 patients and a cumulative reporting rate of 0.80%. Across the clinical study program, MDS has also been reported for 2 patients who did not receive olaparib: one patient that received placebo in Study 19 (0.8% [1/128]) and one patient treated with pegylated liposomal doxorubicin as the comparator in Study 12 (3.1% [1/32]), giving a similar reporting rate.

The first patient was enrolled in the olaparib clinical study program in July 2005 and the first report of MDS was received in 2009. A number of safety measures have been implemented to ensure that AstraZeneca can accurately and carefully monitor this uncommon important potential risk. The olaparib protocols state that any untoward events occurring subsequent to the 30-day follow-up AE reporting period, deemed possibly related to study medication, should be reported as an SAE to AstraZeneca Patient Safety. Investigators have received periodic updates on MDS/AML from either Investigator Safety Letters or 6-monthly Periodic SUSAR Line Listings. Investigators have been reminded regularly of the importance of

reporting any abnormalities suggestive of the development of MDS, including any cases of MDS/AML in patients who have previously participated in studies, by means of a cover letter accompanying the Investigators Brochure, which has been updated five times since 2009. In 2011, a letter was sent to investigators with patients ongoing on olaparib studies to prompt investigators to report any hematological abnormalities suggestive of underlying MDS. Since some reports of MDS/AML have developed after discontinuing treatment with olaparib, additional questions have been included in the regular 3-monthly follow-up calls for overall survival in the phase III studies: investigators are specifically asked if the patient has developed MDS/AML and prompted to report any cases as an SAE.

Sixteen of the patients had a *gBRCA* mutation. The incidence of MDS/AML reported in the patients with known *gBRCA* mutations in the monotherapy pool is 3.2% (12 cases out of 376 *gBRCA* mutated patients in the pool). As a comparison, only the Study 12 patient on pegylated liposomal doxorubicin (PLD) had a *gBRCA* mutation, giving an incidence of 3.3% (1/33) in this study.

Of the 21 cases reported across the development program, 14 have been reported in monotherapy studies and 7 in combination studies. Three of the cases were reported in Study 19 (two on the olaparib arm and one on placebo arm). In 13 cases, the diagnosis was MDS without a report of AML. There were 8 cases of AML. Details for all events of MDS/AML (up to DCO of 02 May 2014) are presented in [Table 48](#) in the appendices.

The median age of onset was 63 years and all but 3 patients had ovarian cancer. Eight patients had a history of previous cancer. The mean time from diagnosis of current cancer to onset of MDS or AML was 62 months. All patients had associated history features that may have contributed to the development of MDS/AML. All had received chemotherapy with DNA damaging agents, including platinum, taxanes and anthracyclines. Many patients received multiple treatment regimens over multiple years and 7 patients had also received radiotherapy. Four patients were treated with olaparib for less than 6 months, 5 patients were treated for between 6 months and 1 year, 4 patients were treated for between 1 and 2 years, and 8 patients were treated for more than 2 years. In the majority of cases, MDS occurred while on treatment with olaparib but in 4 cases the onset of MDS was more than 5 months after olaparib was discontinued.

Epidemiological studies from the literature have indicated a higher risk of therapy related AML in ovarian cancer populations, particularly those receiving alkylating agents and pelvic irradiation, with a wide range of incidence rates. In two recent studies using the US SEER database, Vey et al identified 98 cases of t-AML among 63,359 epithelial ovarian cancer cases, with an overall incidence of 0.15% ([Vay et al 2011](#)), while another SEER-based study in registries representing 9.5% of the US population for years 1975-2008 reported 72 t-AML cases among 23,180 ovarian cancer patients (incidence of 0.31%) ([Morton et al 2013](#)). The SEER data need to be reviewed with caution because MDS is not collected in cancer registries as it is considered pre-malignant and the data from the early episodes are confounded by a higher contemporaneous use of Melphalan, which is no longer prescribed.

MDS and AML are important potential risks that AstraZeneca will continue to actively investigate in the phase III program and post-marketing setting. Additional pharmacovigilance activities will be undertaken to further understand the potential risk of MDS/AML as fully as possible in the context of the benefit to patients with advanced platinum sensitive relapsed ovarian cancers.

Additional safety measures have been incorporated into the phase III study protocols: normal hematological values are required before inclusion into the studies; regular blood tests are required while on treatment to detect hematological abnormalities early and in case of prolonged cytopenias patients are to be referred to a hematologist and bone marrow analysis should be considered. If a diagnosis of MDS is confirmed, study treatment must be discontinued and the event, treatment, course and outcome must be reported as an SAE.

Post-marketing risk-minimization measures for hematological toxicity focus on providing information about the benefit:risk profile to prescribers and patients via the US PI (Warnings and Precautions) and the Patient Information Leaflet. Specifically: Patients should not start treatment with olaparib until they have recovered from hematological toxicity due to prior chemotherapy, and should be followed by monthly blood count monitoring during the first year of treatment. At signs of severe toxicity or blood transfusion dependence, treatment should be interrupted. If the blood parameters remain clinically abnormal after 4 weeks of dose interruption, bone marrow analysis and/or blood cytogenetics are recommended.

New primary Malignancies

Similar to MDS/AML, the development of new primary malignancies is an adverse event of interest that may be related to products that affect DNA repair mechanisms, and of relevance to patients with germline *BRCA* mutations, who are at risk of developing other cancers. As of 02 May 2014, 20 of the 2618 patients who had received olaparib had reported 22 events of a new primary malignancy (other than MDS/AML), giving a cumulative incidence of 0.76% for new primary malignancies. Ten of the cases were non-melanoma skin cancers. The remaining cases were: breast cancer (n=3), breast cancer in situ; lung cancer (n=2) gastric cancer, plasma cell myeloma, malignant melanoma, precursor T-lymphoblastic lymphoma/leukemia, colon cancer and malignant muscle neoplasm (this lesion was present before olaparib treatment). In addition, one patient in the placebo arm of the double blind Study 19 reported a new primary malignancy event of bladder cancer (1/128, [0.78%]). All patients had already previously received various chemotherapy agents including multiple cycles of DNA damaging platinum containing chemotherapies, taxanes, anthracyclines and other alkylating and DNA damaging agents. Four patients were reported to have had prior radiotherapy. Eighteen patients had a documented breast cancer gene mutation (*BRCA 1* or 2). Seven patients had an earlier diagnosis of a previous cancer (ovarian, cervix, breast, peritoneal) prior to their cancer under investigation in the olaparib study.

New primary malignancies will be monitored actively in the phase III program and post-marketing. The US Risk Management Plan states requirement for routine pharmacovigilance practices, signal identification and review for new primary malignancies.

Additional information is to be collected in the Phase III studies to further characterize the nature of the risk.

5.2.5.5 Clinical chemistry, renal and hepatic function

- The clinical chemistry changes observed during Study 19 were generally mild to moderate in severity and required no treatment/dose modification. Increases in blood creatinine have been observed with olaparib, without clinical sequelae. There were no clinically relevant findings for urinalysis.
- Clinical laboratory data for renal function were assessed for Study 19 and the 400 mg bd monotherapy pooled dataset. These data, in conjunction with an assessment of renal /abnormal renal biochemistry AEs, show that olaparib does not appear to induce renal toxicity, although mild elevations in creatinine have been observed with no apparent sequelae. The clinical significance of these mild elevations in creatinine is unknown. The small increases in creatinine observed with olaparib and the rapid onset of the changes observed may indicate that olaparib is an OCT2 inhibitor.
- Maximum overall grades during treatment for key clinical chemistry parameters (ALT, AST, ALP, bilirubin and creatine) are summarized in [Table 46](#) in the appendices.
 - The number of patients with changes to CTCAE grade 3 or 4 values during the study was low and generally similar in the olaparib and placebo groups.
- A detailed assessment of hepatic function laboratory data has been performed across Study 19, the 400 mg bd monotherapy pooled dataset, and in all patients who received any dose of olaparib monotherapy. This evaluation, in conjunction with an assessment of reported hepatobiliary /abnormal hepatic biochemistry AEs did not identify an increased risk of drug-induced liver injury in the olaparib treated patient population.
 - In total, 37/735 patients (5.0%) across the pooled monotherapy dataset reported 57 events from the hepatobiliary disorders or investigations SOC relating to hepatic toxicity. Patients had alternative explanations for the events reported, such as their disease under study eg, bile duct cancer, underlying comorbidities eg, current medical history of chronic cholecystitis or cholestatic jaundice, hepatobiliary obstruction, bile duct stone, hepatic, metastases and subsequent disease progression.
- There were 2 possible cases of Hy's law based on a review of the biochemistry (ie, any elevated aminotransferase (AT) of $\geq 3 \times$ ULN, alkaline phosphatase (AP) $< 2 \times$ ULN and associated with an increase of bilirubin $\geq 2 \times$ ULN) (Patients E0613008 and E0805001).
 - In both cases, there were considered to be other explanations for the abnormalities observed in hepatic function and the cases are not considered to be suggestive of drug-induced liver injury. One patient had dilated

common bile duct with impacted stone at lower end of common bile duct and was diagnosed with cholelithiasis. The other patients had metastatic disease with cholestatic jaundice and elevated alkaline phosphatase.

5.2.5.6 ECG

- Non-clinical studies in rats and dogs showed no evidence of cardiac toxicity following oral dosing of olaparib. From the non-clinical and clinical data available to date the potential for olaparib to cause a clinically significant effect on electrocardiogram (ECG) parameters is considered to be minimal.
- The formal collection of QT data is ongoing in two clinical studies (Study 04 and Study 07) and interim data are currently available from 44 patients. Following multiple dosing (300 mg bd olaparib tablet dose given for 5 consecutive days), there was no indication of a clinically relevant effect of olaparib monotherapy on cardiac repolarization.

5.2.6 Adverse events in special patient populations: age and race

Age

No substantial difference in the safety profile was noticed based on age. AEs of grade ≥ 3 appeared more frequent in patients aged ≥ 65 years (53.4%) than those aged < 65 years (43.4%). Adverse events leading to dose modification were also more frequently reported in patients aged ≥ 65 years (52.7%) than those aged < 65 years (36.6%). No single MedDRA preferred term appeared more frequent in the ≥ 65 years age group than the < 65 years age group. There were no large differences in frequency between the age groups at the system organ class and MedDRA preferred term level for individual AEs of grade ≥ 3 that would account for the difference seen between age groups.

Race

The vast majority (95.6%) of patients who received olaparib in Study 19 were Caucasian. The non-Caucasian group was too small to validly draw conclusion with respect to the influence of race (see [Table 34](#)).

6. ONGOING PHASE III PROGRAM

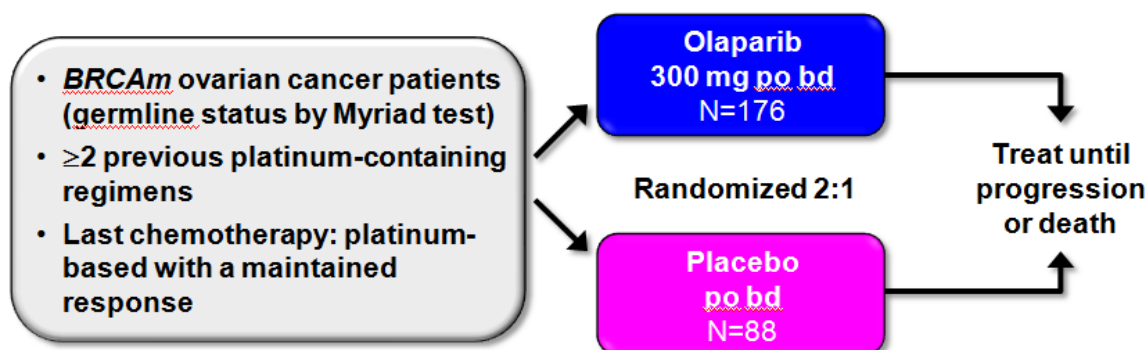
A number of phase III studies are planned/ongoing, all utilizing the 300 mg bd dose of the tablet formulation of olaparib, including the SOLO2 study that will provide confirmatory evidence of the PFS benefit observed in *gBRCAm* patients in Study 19. The selection of the 300 mg bd tablet dose for phase III is discussed in [Section 3.2.2](#)

6.1 SOLO2: confirmatory phase III study

- The SOLO2 study is designed to confirm the benefit of olaparib maintenance therapy in relapsed *BRCAm* ovarian cancer patients. SOLO2, which is led by the European

Network for Gynecological Oncological Trial groups (ENGOT; NCT01874353), replicates many of the main design features of the pivotal phase II Study 19.

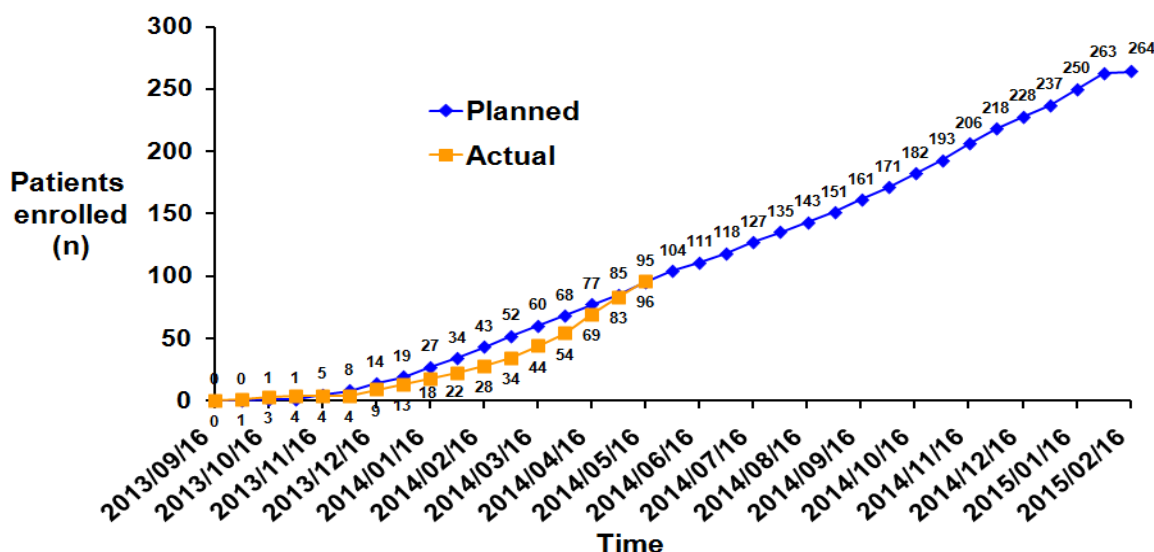
Figure 22 SOLO2 overview



- The primary endpoint of SOLO2 is to determine the efficacy by progression-free survival (PFS) (using blinded independent central review) of olaparib maintenance monotherapy compared with placebo in *BRCAm* relapsed ovarian cancer patients who are in complete or partial response following platinum based chemotherapy.
- Secondary endpoints include overall survival (OS), time from randomisation to second progression (PFS2), time from randomisation to second subsequent therapy or death (TSST) and health-related quality of life (HRQoL), as assessed by the trial outcome index (TOI) of the Functional Assessment of Cancer Therapy – Ovarian (FACT-O).
- The study is sized on having sufficient precision of the estimated PFS Hazard Ratio (HR). Analyses will be performed on a higher number of events than would be required for a powered superiority analysis for both PFS and the secondary endpoint of PFS2; therefore, the power to show superiority for both these endpoints would be >90%. In total 158 events are required to give sufficient precision of the PFS HR. For example, if a HR of 0.2 (similar to the Phase II Study 19) was observed, the 95% CI would be 0.14-0.28. Approximately 264 patients will be recruited (2:1 ratio) so that data maturity for the PFS analysis is approximately 60%. Assuming 18 months non-linear recruitment, 158 PFS events are expected to occur approximately 24 months after the first subject is enrolled in the study (FSI), anticipated to occur by end of 2015. This will be the primary analysis of PFS.
- Patients will be randomised within 8 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and randomisation will be stratified by (1) response to previous platinum chemotherapy (complete response or partial response), and (2) time to disease progression in the penultimate platinum based chemotherapy prior to enrolment (>6 months to 12 months, and >12 months).

- SOLO2 is well underway, and patients will be recruited from Australia, Belgium, Brazil, China, Canada, France, Germany, Israel, Italy, Japan, Netherlands, Poland, Russia, South Korea, Spain, UK and USA. These countries are considered to follow similar ovarian cancer practice to the US. Recruitment is expected to be complete in 1Q2015 (Figure 23).

Figure 23 Recruitment in the confirmatory Phase III SOLO2 study



6.2 Other phase III studies

An additional phase III study (SOLO1) is ongoing in first line ovarian cancer patients in response to platinum containing chemotherapy.

AstraZeneca is also conducting three phase III studies with olaparib tablets to support registration of olaparib in patients with germline *BRCA* breast cancer mutations:

- A phase III, randomized study of olaparib monotherapy vs physician's choice chemotherapy in patients with *BRCAm* recurrent metastatic breast cancer (Study D0819C00003; NCT02000622) conducted with the US Breast Cancer Alliance (Principal Investigator Dr Mark Robson and Memorial Sloan Kettering). Enrolment commenced in March 2014.
- A randomized, open-label, parallel group, multicentre phase III study in collaboration with the Breast Cancer International Group (BIG; Chair Dr Martine Piccart) to assess the impact on pathological complete response rate of adding olaparib to paclitaxel in the neoadjuvant setting in patients with *BRCAm* triple-negative breast cancer (Study D081EC00005). Planned study start is the third quarter of 2014.

- An Intergroup/BIG study (NSABP 9609 NRG) randomized double-blind parallel group placebo-controlled multicentre phase III study, to assess the efficacy and safety of olaparib vs placebo as adjuvant treatment in *BRCAm* high-risk triple-negative breast cancer patients who have completed definitive local and systemic neo/adjuvant treatment (Study D081CC00006; NCT02032823). Enrolment commenced in April 2014.

Phase III studies are also ongoing in patients with gastric and pancreatic cancer, respectively.

7. BENEFIT RISK ASSESSMENT

- Platinum-sensitive relapse of high grade serous ovarian cancer is a serious life-threatening disease for which only repeated lines of chemotherapy (usually platinum-based), gives temporary reprieves.
- There is no FDA approved maintenance treatment for platinum-sensitive relapsed disease. As chemotherapy toxicity prevents its continuation until further relapse, patients who achieve response or disease stabilization are forced to discontinue chemotherapy. Watch and wait is the standard of care.
- Treating during the “watch and wait” period, ie the maintenance period, offers the opportunity to further delay disease relapse and progression, the symptoms associated with relapse and the use and toxicity resulting from conventional cytotoxic chemotherapy.
- Olaparib is a first-in-class PARP inhibitor which selectively exploits deficiencies in DNA homologous recombination repair pathway in cancer cells, an effect predicted to be further enhanced in patients with germline mutation of the *BRCA1* or *BRCA2* genes.
- In a well conducted placebo-controlled study, olaparib demonstrated an 83% reduction in the risk of relapse or death in women with *gBRCA* mutated platinum-sensitive relapsed high-grade ovarian cancer. Median PFS increased by 7.1 months, from 4.1 months in placebo-treated patients to 11.2 months in the olaparib arm.
- Olaparib safety was well characterized, associated with an increase in mostly low grade nausea/vomiting (amenable to simple treatment), anemia (requiring blood monitoring and in some cases a blood transfusion), and fatigue of low grade. Long term olaparib treatment was possible (24% and 14% of all patients on treatment at year 2 and 3, respectively for olaparib compared with 4% and 2% for placebo) and discontinuations due to AEs were uncommon (5%).
- Germline *BRCA* mutation status is routinely determined on blood, and AstraZeneca is working with Myriad Genetics Laboratories Inc. to deliver an FDA approved companion diagnostic for olaparib.

- SOLO2 (the proposed confirmatory Phase III study) is well underway, primarily in collaboration with ENGOT, and should complete accrual by 1Q2015. SOLO2 aims to confirm with precision the magnitude of PFS benefit in prospectively selected *BRCAm* patients with platinum-sensitive relapsed high-grade serous ovarian cancer. Overall survival is a secondary endpoint, as are quality of life and other measures. AstraZeneca commits to work with the Agency to review the totality of the evidence once the results of the SOLO2 study are available (by mid-2016). If not confirmatory in nature, AstraZeneca will consequently abide by the results and take the necessary actions, which could include withdrawal of the NDA. A large Phase III program across various tumor types is underway, with some studies under US NCI/ Intergroup sponsorship.

Unmet need

Ovarian cancer is a serious, life-threatening disease for which new medicines are needed. The current mainstay of therapy consists of multiple lines of chemotherapy, where a platinum agent is routinely employed. However, despite good initial responses in many platinum-sensitive patients, all patients will relapse and the platinum-free interval becomes shorter in duration with each retreatment, with the disease ultimately becoming platinum-resistant. As such, relapsed ovarian cancer is considered incurable. Patients may also become intolerant of treatment due to the cumulative toxicities of platinum-based therapies. No maintenance therapy is approved for PSR ovarian cancer patients, and a ‘watch and wait’ strategy is the standard of care, with active surveillance throughout remission but no active treatment. Olaparib meets the unmet need for an active and well-tolerated maintenance therapy, by building on the initial benefits of platinum-based chemotherapy through a clinically relevant delay in disease progression, resulting in a clinically meaningful prolongation of the platinum-free interval, need for and time to subsequent cytotoxic chemotherapy lines, along with delaying the toxicity and morbidity associated with chemotherapy.

The biology of PARP predicts for benefit in *BRCAm* patients, regardless of whether their mutation is detected by blood (germline) or tumor testing, and this is borne out by the findings in Study 19. However, the required companion diagnostic will be based on a blood test (the Myriad Integrated *BRACAnalysis*[®] test) for the detection of germline *BRCA* mutations. Therefore the risk benefit focuses on findings in the *gBRCAm* subgroup, in accordance with the proposed indication.

Clinical benefit of olaparib in patients with PSR *gBRCA* mutated (*gBRCAm*) ovarian cancer

Olaparib maintenance therapy has demonstrated in a well-controlled randomized phase II study (Study 19) a clinically meaningful and highly statistically significant prolongation of PFS in the subgroup of 96 patients with *gBRCAm* ovarian cancer (PFS HR=0.17; 7.1 month prolongation of median progression-free survival over placebo). This finding in the *gBRCAm* subgroup is in the context of a positive trial that met its primary PFS endpoint in the overall population of all patients, unselected for *BRCA* mutation.

Exploratory analysis provides reassurance that olaparib maintenance therapy does not adversely affect subsequent therapy, with a 7 month prolongation of median time from randomization to second subsequent therapy or death (HR 0.43) compared with placebo, and fewer patients receiving subsequent courses of cytotoxic chemotherapy (57% vs 86% for olaparib and placebo arms, respectively). There was no difference in overall survival or health-related quality of life between treatment arms.

A confirmatory phase III study (SOLO2) in *BRCAm* patients is ongoing, with data expected in late 2015. SOLO2 is designed to precisely confirm the magnitude of PFS benefit seen in the *BRCAm* subgroup in Study 19, which is the basis of this application for accelerated approval.

Safety and tolerability of olaparib

The tolerability profile of olaparib is well characterized and suitable for long-term dosing as a maintenance therapy following platinum-based chemotherapy, until disease progression.

Safety findings were consistent in Study 19 (N=264 patients, 136 on olaparib), in the larger pool of patients who received 400 mg bd olaparib monotherapy (N=735 patients) and the population of all patients who have received olaparib (N=2618 as of 02 May 2014).

Additional safety data will become available from ongoing phase III studies, including a further 2683 patients (planned enrolment) *BRCAm* patients. This broad phase III program includes 264 and 344 *BRCAm* patients from SOLO2 and SOLO1, respectively, which will provide the most relevant randomized, controlled safety data being generated for *gBRCAm* ovarian cancer patients in the maintenance treatment setting.

Long-term tolerability to olaparib maintenance therapy has been demonstrated, with 40%, 24% and 14% of all patients (45%, 25% and 17% in the *gBRCA* subgroup) in the olaparib group remaining on treatment at 1 year, 2 years and 3 years, respectively in Study 19. Most patients remained on treatment until disease progression, with only a small number of patients permanently discontinuing study treatment due to AEs (5.1% with olaparib vs 1.6% with placebo overall; 9.4% vs 0% in the *gBRCA* subgroup).

The common AEs of nausea, vomiting, fatigue and anemia are routinely managed by oncologists treating cancer patients. The low grade and intermittent nature of these events means that nausea and vomiting can be treated empirically and anti-emetic prophylaxis is not required. Hematological changes including anemia should be monitored routinely using standard assessments of hematological laboratory parameters, as is routine for patients receiving anti cancer therapies. Where necessary, AEs can be managed by interrupting or reducing the olaparib dose, treating symptomatically with standard procedures (eg, antiemetics for nausea and vomiting, occasional blood transfusions for anemia) or in rare cases by permanently discontinuing olaparib treatment.

MDS/AML are considered AEs of special interest as they may be related to agents that affect DNA repair, including chemotherapy. These events have been seen in less than 1% of patients who received olaparib. These events will be actively monitored in the ongoing phase III studies, including prompted follow-up.

Conclusions

Olaparib, as first-in-class PARP inhibitor, offers the potential to be the first personalized treatment option for women with relapsed ovarian cancer associated with a mutation in germline *BRCA1* and/or *BRCA2*. The data presented in this briefing document demonstrate that, based on phase II data and as predicted by the biology, olaparib is an active and well-tolerated agent with a positive benefit:risk ratio and enhanced efficacy benefit (HR=0.17) in patients with PSR germline *BRCA* (*gBRCA*)m ovarian cancer.

Smaller but still statistically significant benefit was also seen in all patients (HR=0.35) and in the subgroup of patients designated as *gBRCA* wildtype/VUS (HR=0.50). This is consistent with the understanding that the entire study population in Study 19 was enriched for the HRD phenotype, by definition of platinum sensitivity.

The combination of olaparib with chemotherapy followed by continuation maintenance (olaparib) treatment (as tested in Study 41), is not considered appropriate for olaparib in patients with ovarian cancer. Administration of olaparib as a maintenance monotherapy to *gBRCA*m patients after completion of platinum-based chemotherapy, or switch maintenance therapy (as in Study 19) is considered the optimal treatment strategy.

AstraZeneca considers that this phase II olaparib data, combined with the phase III post-approval commitment, meet the criteria for accelerated approval ([FDA 2013](#)) based on the following:

- Ovarian cancer is a serious, life-threatening disease for which new medicines are needed. Specifically, there is an unmet need for a tolerable therapy that can actively maintain the chemotherapy response, whilst minimizing the toxicity burden for patients by delaying the need for next-line chemotherapy and its associated toxicities. The ability to continue to actively treat a patient until disease progression maximizes the period of remission/stabilization following chemotherapy and is achievable with olaparib.
- The results of the phase II randomized placebo-controlled maintenance study (Study 19), a well-controlled randomized study, demonstrated a statistically significant PFS benefit (HR 0.17 in the *gBRCA*m subgroup) with median time to progression extended by 7.1 months compared with placebo. This represents a direct clinically meaningful benefit and highly statistically significant improvement over the current standard of care, which is active surveillance post-chemotherapy.
- The benefit:risk profile for olaparib in *gBRCA*m ovarian cancer is positive, and olaparib has a favorable therapeutic index with a tolerability profile that allows prolonged administration.
- Olaparib maintenance therapy demonstrated no detrimental impact on HRQoL outcomes compared with placebo.

- The *gBRCAm* population is easily identifiable by a readily available blood-based test (the Clinical Laboratory Improvement Amendment [CLIA]-accredited Myriad Integrated *BRCA*Analysis[®] test), available since 1994. AstraZeneca is working with Myriad to gain approval (PMA) for a companion diagnostic, based on this test.
- The phase III study (SOLO2) is designed to confirm the clinical benefit of olaparib maintenance therapy in relapsed *BRCAm* ovarian cancer patients. The study is ongoing and expected to be fully enrolled with 264 patients in 1Q2015, with data expected in late 2015 and submission and regulatory review during the first half of 2016.

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Author correction to “Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J et al. *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* 2012;30:2654-63.” *J Clin Oncol* 2012;30:4180.

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9. APPENDIX 1: ANALYSES UNDERTAKEN TO CONFIRM RELIABILITY AND ROBUSTNESS OF PFS ANALYSES IN STUDY 19

9.1 Overview

Since there are unique sources of biases related to progression-free survival (PFS), a number of sensitivity/supportive analyses have been performed to assess the reliability and robustness of the Study 19 PFS results observed for the ITT population and *gBRCA* subgroup.

Based on all the different sensitivity analyses applied to the Study 19 data, there is no evidence to suggest that the primary PFS result has been impacted by a meaningful amount of bias through differential scanning, censoring or statistical analysis method.

Therefore, AstraZeneca consider the primary PFS analysis results to be a robust assessment of the treatment benefit for olaparib compared with placebo in patients with platinum sensitive relapsed serous ovarian cancer following treatment with two or more platinum containing regimens.

9.2 Summary of methods

The following analyses were performed in order to assess the reliability and reproducibility of the Study 19 PFS results for the ITT population and *gBRCA* subgroups:

1. Attrition bias assessment –censoring rules
2. Attrition bias assessment – blinded independent central review (BICR)
3. Evaluation time bias assessment
4. Early censoring assessment
5. Supportive analyses using the earlier of CA-125 or RECIST progression
6. Supportive analyses using alternative statistical analyses (stratified and unstratified log-rank test).

Definitions for each analysis are provided in Section 9.3, analysis results are provided in Section 9.4 and conclusions are outlined in Section 9.5.

9.3 Analysis definitions

9.3.1 PFS overview

PFS is defined as the time from randomization to the earlier date of radiological progression (per RECIST criteria) or death by any cause in the absence of objective progression.

Patients who have not progressed or died at the time of the data cut-off for the primary PFS analysis will be censored at the latest date of the Target Lesion/Non-Target Lesion assessment of their last evaluable objective tumor assessment.

Patients who progress, or die in the absence of progression, immediately following two or more consecutive non-evaluable (NE) objective tumour assessments, will be censored at the date of the last evaluable assessment. For Study 19 there were no patients for whom this censoring rule applied.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression and their PFS time will be derived as defined above. For Study 19, there were two patients who had subsequent therapy information recorded prior to progression.

PFS was analyzed using a Cox proportional hazards model with factors for

- Treatment (olaparib vs. placebo)
- Time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment)
- Objective response (complete response [CR] or partial response [PR], in the last platinum therapy prior to enrolment)
- Jewish descent (yes or no).

9.3.2 Supportive sensitivity assessment details

9.3.2.1 Attrition bias assessment

Attrition bias assessment determines whether the rate and nature of censoring has resulted in bias (eg, handling of censoring for patient taking subsequent therapies prior to progression, censoring based on missed visits etc).

Censoring rules

To assess attrition bias, the primary PFS analysis was repeated except all PFS events (progressions and death) were included regardless of non-evaluable/missed tumor assessments (ie, progressions or deaths following >2 non-evaluable assessments were included as events). For Study 19 there were no patients for whom this censoring rule applied.

In addition, patients who received a subsequent therapy prior to progression were censored at their last evaluable RECIST assessment prior to starting the subsequent therapy. For Study 19, there were two patients who had subsequent therapy information recorded prior to progression.

Blinded independent central review

A retrospective blinded independent central review of scans was performed as a sensitivity analysis to confirm the robustness of the primary PFS analysis. The analysis of the independent central review data used the same methodology as the primary PFS analysis.

9.3.2.2 Evaluation time bias assessment

To assess evaluation time bias, an interval censored approach was used based on the methodology by Sun and Zhao ([Sun et al 2005](#)). The methodology uses generalized log-rank tests for interval-censored failure time data which are robust to differences in assessment schedules. The p-values for treatment group comparisons were calculated using this methodology. The associated hazard ratios were estimated from a Cox model that analyses the midpoint of the assessment interval. The decision to use this analysis was based on research produced by the PhRMA PFS Expert Group: even in situations where assessments are made twice as frequently in the one group interval censored approaches, unlike a conventional log-rank, type I error was only inflated to 2.8% 1-sided ([Sun et al 2010](#) and summarised in [Stone et al 2011](#), Table 4).

A second evaluation time bias was also completed. This “Evaluation time bias as per scheduled visit” (Tables B and C of FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics 2007; [FDA 2007](#)) analysis uses a PFS time calculated for each patient using only scheduled RECIST assessments for both progressions and censored observations with a 1 week window around each scheduled assessment. This means that if an assessment occurred after the 1 week window the PFS time is moved to the next scheduled visit. So for example; if a patient has an assessment at Week 14 in this evaluation time bias assessment they would be given a PFS time of 24 weeks. For the one patient who had a death prior to progression, their PFS time remained the same. The censoring in this analysis remained as per the primary PFS analysis.

The primary PFS analysis was repeated (a Cox PH model with factors for treatment, ethnic descent, platinum sensitivity and response to final platinum therapy) for the evaluation time bias assessment as per scheduled visit analysis, using the new variable scheduled visit PFS variable.

9.3.2.3 Early censoring assessment (Rothmann)

To evaluate the impact of early censoring, patients without progression who did not have scans performed up until the data cut-off (DCO), two analyses of PFS were performed as outlined by Rothmann ([Rothmann et al 2013](#)). The first was to assign an event to any patient whose PFS censoring was due to lost to follow-up, withdrawal of consent or any patients censored more than 12 weeks prior to data cut-off for other reasons. The second analysis was a repeat of the first except assigning of events only to early censored patients who were randomized to receive Olaparib treatment.

9.3.2.4 Supportive analyses using the Earlier of CA-125 or RECIST Progression

Time to CA-125 or RECIST progression was analyzed in the same way as the primary analysis of PFS, adjusting for the same set of covariates.

9.3.2.5 Supportive analyses using the alternative statistical analyses

PFS was analyzed using an unstratified log-rank test and a log rank test stratified by the randomisation stratification factors:

- time to disease progression (>6-12 months and >12 months, in the penultimate platinum therapy prior to enrolment)
- objective response (CR or PR, in the last platinum therapy prior to enrolment)
- Jewish descent (yes or no).

9.4 Summary of results

9.4.1 PFS Supportive and Sensitivity Analyses -ITT

The results of the PFS supportive and sensitivity analyses are presented below.

Table 30 PFS Supportive and Sensitivity analyses - ITT

Analysis	No. Events: No. Patients	PFS HR	95% CI
Primary PFS	Olaparib: 60:136 (44%) Placebo: 94:129 (73%)	0.35	0.25-0.49
Attrition bias Censoring rules	Olaparib: 59:136 (43%) Placebo: 94:129 (73%)	0.35	0.25-0.48
Attrition bias Blinded Independent Central review	Olaparib: 54:133 (41%) Placebo: 81:127 (64%)	0.39	0.28-0.56
Evaluation time bias Interval Censoring	Olaparib: 60:136 (44%) Placebo: 94:129 (73%)	0.39	0.28-0.54
Evaluation time bias Scheduled visit method	Olaparib: 60:136 (44%) Placebo: 94:129 (73%)	0.37	0.26-0.51
Early censoring (Rothmann) All early censoring as an event	Olaparib: 76:136 (56%) Placebo: 110:129 (85%)	0.40	0.29-0.54
Early censoring (Rothmann) Olaparib early censoring as an event	Olaparib: 76:136 (56%) Placebo: 94:129 (73%)	0.46	0.34-0.63
Earlier of CA-125 or RECIST progression	Olaparib: 66:136 (49%) Placebo: 106:129 (82%)	0.35	0.25-0.47

Table 30 PFS Supportive and Sensitivity analyses - ITT

Analysis	No. Events: No. Patients	PFS HR	95% CI
Statistical analyses	Olaparib: 60:136 (44%)	0.36	0.25-0.50
Stratified log rank test	Placebo: 94:129 (73%)		
Statistical analyses	Olaparib: 60:136 (44%)	0.37	0.26-0.51
Un-stratified log-rank test	Placebo: 94:129 (73%)		

A hazard ratio of <1 favors olaparib. Data cut-off: 30 June 2010

CI Confidence interval; FAS Full analysis set; HR Hazard ratio; PFS Progression free survival.

**(Rothmann et al 2013) Evaluating and Adjusting for Premature Censoring of Progression-Free Survival, Journal of Biopharmaceutical Statistics, 23:5, 1091-1105.

The table below summarizes the progression status information relevant for the early censoring analyses.

Table 31 PFS Early Censoring (ITT)

Progression Status	Olaparib	Placebo	Total
Total	136	129	265
Events	60 (44%)	94 (73%)	154 (58%)
Censored			
Alive and progression free	60 (44%)	19 (15%)	79 (30%)
>12 weeks before DCO	16 (12%)	16 (12%)	32 (12%)

9.4.2 PFS supportive and sensitivity analyses - *gBRCAm*

The results of the PFS supportive and sensitivity analyses are presented below.

Table 32 PFS supportive and sensitivity analyses – *gBRCAm*

Analysis	No. Events: No. Patients	PFS HR	95% CI
Primary PFS	Olaparib: 17:53 (32.1%) Placebo: 33:43 (76.7%)	0.17	0.09-0.31
Attrition bias	Olaparib: 17:53 (32.1%)	0.17	0.09-0.31
Censoring rules	Placebo: 33:43 (76.7%)		
Attrition bias	Olaparib: 15:53 (28.3%)	0.25	0.13-0.49
Blinded Independent Central review	Placebo: 26:42 (61.9%)		
Evaluation time bias	Olaparib: 17:53 (32.1%)	0.20	0.11-0.36
Interval Censoring	Placebo: 33:43 (76.7%)		

Table 32 PFS supportive and sensitivity analyses – *gBRCAm*

Analysis	No. Events: No. Patients	PFS HR	95% CI
Evaluation time bias	Olaparib: 17:53 (32.1%)	0.20	0.11-0.36
Scheduled visit method	Placebo: 33:43 (76.7%)		
Early censoring (Rothmann**)	Olaparib: 26:53 (49%)	0.25	0.15-0.43
All early censoring as an event	Placebo: 40:43 (93%)		
Early censoring (Rothmann**)	Olaparib: 26:53 (49%)	0.30	0.17-0.52
Olaparib early censoring as an event	Placebo: 33:43 (77%)		
Earlier of CA-125 or RECIST progression	Olaparib: 21:53 (40%)	0.24	0.13-0.43
	Placebo: 36:43 (84%)		
Statistical analyses	Olaparib: 17:53 (32%)	0.13	0.07-0.26
Stratified log rank test	Placebo: 33:43 (77%)		
Statistical analyses	Olaparib: 17:53 (32%)	0.17	0.09-0.31
Un-stratified log-rank test	Placebo: 33:43 (77%)		

A hazard ratio of <1 favors olaparib. Data cut-off: 30 June 2010

CI Confidence interval; *gBRCAm* Germline *BRCA* mutated; HR Hazard ratio; PFS Progression free survival.

**[Rothmann et al; \(2013\)](#) Evaluating and Adjusting for Premature Censoring of Progression-Free Survival, Journal of Biopharmaceutical Statistics, 23:5, 1091-1105. [Table 4](#) summaries the progression status information relevant for the Early Censoring analyses

Table 33 PFS early censoring – *gBRCAm*

Progression Status	Olaparib	Placebo	Total
Total	53	43	96
Events	17 (32%)	33 (77%)	50 (52.1%)
Censored			
Alive and progression free	27 (51%)	3 (7%)	30 (31%)
>12 weeks before DCO	9 (17%)	7 (16%)	16 (17%)

9.5 Conclusions

- The sensitivity analyses assessing potential evaluation time bias and attrition bias support the result of the primary PFS analysis in both the ITT population and *gBRCAm* subgroup, indicating that differential scanning or differential censoring is not a concern for the Study 19 data.

- The observed relative treatment benefit and statistical significance in favor of olaparib for the ITT is maintained even for the worst case scenario analyses, which is likely to be biased against olaparib.
- The results of using the earlier of CA-125 or RECIST progression assessment for the ITT population and *gBRCAm* subgroup are consistent with the primary PFS analysis.
- The results of the analysis of PFS using a different statistical method are consistent with the primary PFS analysis for the ITT population and *gBRCA* subgroup.
- Therefore, AstraZeneca consider the primary PFS analysis results to be a robust assessment of the treatment benefit for olaparib compared with placebo in patients with platinum sensitive relapsed serous ovarian cancer following treatment with two or more platinum containing regimens.

10. APPENDIX 2: SUPPLEMENTARY DATA PRESENTATIONS

Table 34 Summary of demographic characteristics in Study 19: ITT

	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
Age			
n	136	129	265
Mean (standard deviation)	58.9 (11)	58.5 (10)	58.7 (10)
Median (range)	58.0 (21 to 89)	59.0 (33 to 84)	59.0 (21 to 89)
Age classification (years), n (%)			
<50	30 (22)	20 (16)	50 (19)
≥50 to <65	61 (45)	74 (57)	135 (51)
≥65	45 (33)	35 (27)	80 (30)
Race, n (%)			
White	130 (96)	126 (98)	256 (97)
Black or African American	2 (1)	1 (1)	3 (1)
Asian	2 (1)	2 (2)	4 (2)
Other	2 (1)	0	2 (1)
Ethnic population, n (%)			
Jewish descent ^a			
No	115 (85)	112 (87)	227 (86)
Yes	21 (15)	17 (13)	38 (14)

Table 34 Summary of demographic characteristics in Study 19: ITT

	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
Ashkenazi Jewish	17 (13)	12 (9)	29 (11)
Sephardic Jewish	1 (1)	1 (1)	2 (1)
Mizrahim Jewish	2 (1)	1 (1)	3 (1)
Other	0	3 (2)	3 (1)
Missing	1 (1)	0	1 (<1)

^a One patient was classified as not of Jewish descent at the previous data cut-off (30 June 2010) and is now classified as being of Jewish (Ashkenazi) descent.
bd Twice daily; ITT intent to treat.
Data cut-off: 26 November 2012.

Table 35 Summary of patient characteristics at baseline in Study 19: ITT

	Number (%) of patients		
	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
ECOG performance status			
(0/1) Normal/restricted activity	133 (98)	125 (97)	258 (97)
(2) In bed ≤50% of the time	1 (1)	2 (1)	3 (1)
Unknown	2 (1)	2 (1)	4 (2)
Primary tumor location			
Ovary	119 (88)	109 (84)	228 (86)
Fallopian Tube	3 (2)	3 (2)	6 (2)
Primary peritoneal	14 (10)	16 (12)	30 (11)
Other	0	1 ^d (1)	1 ^d (<1)
Tumor grade			
Well Differentiated (G1)	0	0	0
Mod. Differentiated (G2)	36 (26)	34 (26)	70 (26)
Poorly Differentiated (G3)	97 (71)	89 (69)	186 (70)
Undifferentiated (G4)	2 (1)	4 (3)	6 (2)
Unassessable (GX)	1 (1)	2 (2)	3 (1)
FIGO stage ^a			
Stage IB	0	1 (1)	1 (<1)

Table 35 Summary of patient characteristics at baseline in Study 19: ITT

	Number (%) of patients		
	Olaparib 400 mg bd n=136	Placebo n=129	Total n=265
Stage IC	3 (2)	3 (2)	6 (2)
Stage II	1 (1)	0	1 (<1)
Stage IIA	2 (1)	1 (1)	3 (1)
Stage IIB	3 (2)	1 (1)	4 (2)
Stage IIC	5 (4)	6 (5)	11 (4)
Stage III	10 (7)	7 (5)	17 (6)
Stage IIIA	4 (3)	3 (2)	7 (3)
Stage IIIB	8 (6)	12 (9)	20 (8)
Stage IIIC	81 (60)	76 (59)	157 (59)
Stage IV	17 (13)	17 (13)	34 (13)
Unknown	2 (1)	2 (1)	4 (2)
Platinum sensitivity ^b			
>6 - ≤12 months	53 (39)	54 (42)	107 (40)
>12 months	83 (61)	75 (58)	158 (60)
Objective response ^c			
CR	57 (42)	63 (49)	120 (45)
PR	79 (58)	66 (51)	145 (55)

^a FIGO stage was defined at diagnosis not at baseline for this study.

^b Platinum sensitivity = time to progression after the completion of platinum therapy. Note: Platinum sensitivity refers to the penultimate platinum not the platinum regimen that was just completed by the patient. There were 4 patients where platinum sensitivity could not be confirmed (E1701004, E1401001, E0709001 and E0804006); for these patients the category of platinum sensitivity entered on the case report form was used for the analysis covariate (time to progression on penultimate therapy).

^c Objective Response: CR = Patients with no target lesions and no non-target lesions at baseline; PR = Patients with target lesions and/or non-target lesions at baseline. Note: This is the response from the platinum regimen just prior to therapy. Data for 1 patient who did not receive platinum therapy are also included.

^d Patient E1801012 had location of Other – FIMBRIA (Appendix 12.2.4.5).

CR Complete response; ECOG Eastern Co-operative Oncology Group; ITT intent to treat; FIGO Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynecology and Obstetrics); PR Partial response.

Data cut-off: 30 June 2010.

Table 36 Supportive clinical studies that contributed to the overall assessment of clinical efficacy of olaparib

Type of study	Study identifier, status	Objective(s) of the study	Study design/ type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Patient population
Key supportive studies						
Efficacy, safety	Study 41 Completed	To compare the efficacy of olaparib when given in combination with paclitaxel and carboplatin followed by olaparib monotherapy maintenance vs paclitaxel and carboplatin alone without maintenance, by assessment of PFS (independent central review)	Ph II, open-label, randomized, multicentre, combination with carboplatin and paclitaxel. Combination phase (6 cycles) followed by maintenance phase	Olaparib 200 mg bd capsule (oral) in combination with Paclitaxel 175 mg/m ² iv (21-day cycle) Carboplatin AUC4 iv (21-day cycle) followed by 400 mg bd capsule (oral) as maintenance Paclitaxel 175 mg/m ² iv (21-day cycle) Carboplatin AUC6 iv (21-day cycle)	162/156	Patients with platinum-sensitive serous ovarian cancer following treatment with ≤ 3 platinum-containing regimens
Efficacy, safety, PK	Study 12 Completed	To compare the efficacy of 2 different dose levels of olaparib with pegylated liposomal doxorubicin in patients with advanced <i>BRCA1</i> or <i>BRCA2</i> associated ovarian cancer, assessed by PFS	Ph II, open-label, randomized, active control, multicentre	Olaparib 200 mg bd or 400 mg bd capsule (oral) PLD 50 mg/m ² iv at initial rate of 1 mg/min every 4 wks	97/96	Patients with advanced <i>gBRCA1</i> - or <i>gBRCA2</i> -associated ovarian cancer with partially platinum-sensitive or platinum-resistant disease (disease that recurred or progressed within 12 months of the most recent platinum-based chemotherapy)
Other supportive studies						
Efficacy, safety	Study 20 Completed	To determine ORR of olaparib (by RECIST) in known <i>BRCA</i> or high-grade serous/undifferentiated ovarian cancer and known <i>BRCA</i> or triple negative breast cancer including enrichment for tumors with <i>BRCA</i> mutations	Ph II, open-label, non-comparative, multicentre	Olaparib 400 mg bd capsule (oral)	91/90	Patients with <i>gBRCA</i> or recurrent high-grade serous/undifferentiated tubo-ovarian carcinoma and <i>gBRCA</i> or triple negative breast cancer

Table 36 Supportive clinical studies that contributed to the overall assessment of clinical efficacy of olaparib

Type of study	Study identifier, status	Objective(s) of the study	Study design/ type of control	Test products, dosage regimen, route of administration	No. of subjects randomized/ treated	Patient population
Efficacy, safety	Study 42 Completed	To assess the efficacy of oral olaparib in patients with advanced cancer who had confirmed genetic <i>BRCA1</i> and/or <i>BRCA2</i> mutation by assessment of tumor response	Ph II, open-label, non-comparative, multicentre	Olaparib 400 mg bd capsule (oral)	317/298	Patients with advanced cancers with confirmed <i>gBRCA1</i> - and/or <i>gBRCA2</i> -mutations
Efficacy, safety, PK	Study 09 Completed	To assess the efficacy of olaparib at two dose levels in terms of objective tumor response rate when administered orally to patients with <i>BRCA1</i> - or <i>BRCA2</i> - associated ovarian cancer	Ph II, open-label, non-comparative, multicentre	Olaparib 100 mg bd and 400 mg bd capsules (oral)	58/57	Patients with advanced <i>gBRCA1</i> - or <i>gBRCA2</i> -associated ovarian cancer
PK, PD, safety, efficacy	Study 24 Ongoing	Bioavailability of olaparib tablet formulation compared to capsule formulation; safety and tolerability of capsule and tablet formulations at various doses	Ph I, randomized, 2 period, cross-over, multicentre, relative BA (tablet vs capsule). Followed by tablet dose escalation phase (to establish MTD), and expansion phase (to compare efficacy and tolerability of tablet vs capsule)	Bioavailability phase: single dose olaparib (oral): 50, 100, 400 mg capsule; 25, 50, 200 mg tablet. Tablet dose escalation and expansion: olaparib 400 mg bd capsule (oral); olaparib 200, 250, 300, 350, 400, 450 mg bd tablet (oral)	135/134	Patients with advanced solid tumors Patients with <i>gBRCA</i> breast and ovarian cancer recruited into the expansion
PK, PD, safety, efficacy	Study 02 Completed	To determine the safety, tolerability, DLT, PARP inhibitory dose range and MTD of olaparib when administered orally to patients with advanced solid tumors	Ph I, FTIM, multicentre, PK and biological evaluation. Two phases: dose escalation and <i>BRCA</i> expansion	Dose escalation: Olaparib 10 mg od to 600 mg bd capsule (oral). Expansion: Olaparib 200 mg bd capsule (oral)	Overall: 98/98 Expansion phase: 52/52	Patients with advanced solid tumors Expansion in patients with <i>gBRCAm</i> status, including <i>gBRCAm</i> ovarian cancer

AUC Area under plasma concentration-time curve; BA Bioavailability; bd Twice daily; *BRCA* breast cancer susceptibility gene; CSR Clinical study report; DLT Dose-limiting toxicity; *gBRCA* Germline *BRCA*; *gBRCAm* Germline *BRCA* mutated; iv Intravenous; FTIM First time in man; MTD Maximum tolerated dose; od Once daily; ORR Objective response rate; OS Overall survival; PARP Polyadenosine 5'diphosphoribose polymerase; PD Pharmacodynamic; PFS Progression-free survival; Ph Phase; PK Pharmacokinetics; PLD Pegylated liposomal doxorubicin; RECIST Response Evaluation Criteria in Solid Tumors; wks Weeks

Table 37 Most common AEs (>2%) leading to temporary dose interruptions and dose reduction – Study 19

Preferred Term	Safety Analysis		<i>gBRCAm</i> patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
AEs leading to temporary dose interruptions				
TOTAL	47 (34.6)	12 (9.4)	16 (30.2)	2 (4.7)
Vomiting	11 (8.1)	1 (0.8)	5 (9.4)	0
Nausea	7 (5.1)	1 (0.8)	3 (5.7)	0
Fatigue	6 (4.4)	2 (1.6)	0	0
Abdominal pain	5 (3.7)	2 (1.6)	0	1 (2.3)
Anemia	5 (3.7)	0	2 (3.8)	1 (2.3)
Diarrhea	4 (2.9)	1 (0.8)	2 (3.8)	0
Dyspnea	4 (2.9)	0	2 (3.8)	0
Neutropenia	3 (2.2)	0	3 (5.7)	0
Leukopenia	3 (2.2)	0	2 (3.8)	0
AEs leading to dose reductions				
TOTAL	28 (20.6)	3 (2.3)	7 (13.2)	1 (2.3)
Anemia	4 (2.9)	1 (0.8)	1 (1.9)	0
Fatigue	5 (3.7)	0	3 (5.7)	0
Nausea	5 (3.7)	0	2 (3.8)	0
Vomiting	4 (2.9)	1 (0.8)	1 (1.9)	0
Asthenia	3 (2.2)	0	0	0

Table 38 Number (%) of patients reported with AEs leading to discontinuation of study treatment: Study 19, Safety Analysis Set

System Organ Class/ Preferred term	All patients		<i>gBRCAm</i>	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Any AE leading to discontinuation	7 (5.1)	2 (1.6)	5 (9.4)	0
Thrombocytopenia	1 (0.7)	0	1 (1.9)	0
Palpitations	1 (0.7)	0	1 (1.9)	0
Nausea	1 (0.7)	1 (0.8)	0	0
Small intestinal obstruction	1 (0.7)	0	0	0
Cholestatic jaundice	1 (0.7) ^a	0	0	0

Table 38 **Number (%) of patients reported with AEs leading to discontinuation of study treatment: Study 19, Safety Analysis Set**

System Organ Class/ Preferred term	All patients		<i>gBRCAm</i>	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Herpes Zoster	1 (0.7)	0	1 (1.9)	0
Myalgia	1 (0.7)	0	1 (1.9)	0
Haemorrhagic stroke	1 (0.7)	0	1 (1.9)	0
Erythematous rash	1 (0.7)	0	1 (1.9)	0
Pruritic rash	0	1 (0.8)	0	0

a Cholestatic jaundice was subsequently classified as disease progression.
Patients with multiple AEs leading to discontinuation reported are counted once for each preferred term.
Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Table 39 **Number (%) patients with reported AEs leading to discontinuation of olaparib (≥2 patients in either group) - 400 mg bd monotherapy pool**

System Organ Class/ Preferred term	All patients (advanced solid tumors) N=735	<i>BRCAm</i> ovarian cancer N=397 ^a
Any AE leading to discontinuation	43 (5.9)	23 (5.8)
Blood and lymphatic system disorders	9 (1.2)	5 (1.3)
Anemia	3 (0.4)	2 (0.5)
Neutropenia	3 (0.4)	1 (0.3)
Thrombocytopenia	4 (0.5)	3 (0.8)
Gastrointestinal disorders	20 (2.7)	11 (2.8)
Abdominal distension	2 (0.3)	1 (0.3)
Abdominal pain	3 (0.4)	3 (0.8)
Diarrhea	3 (0.4)	0
Intestinal obstruction	3 (0.4)	2 (0.5)
Nausea	5 (0.7)	3 (0.8)
Small intestinal obstruction	3 (0.4)	1 (0.3)
Vomiting	4 (0.5)	3 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	3 (0.4)	0

Table 39 **Number (%) patients with reported AEs leading to discontinuation of olaparib (≥2 patients in either group) - 400 mg bd monotherapy pool**

System Organ Class/ Preferred term	All patients (advanced solid tumors) N=735	<i>BRCAm</i> ovarian cancer N=397^a
Pleural effusion	2 (0.3)	0

a *BRCA* mutation status determined by blood and/or tumor testing.
Sorted alphabetically by SOC and PT. Patients with multiple AEs leading to discontinuation reported are counted once for each SOC/PT.
Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Table 40 **Number (%) of patients who had at least one AE in any category – 400 mg bd monotherapy pool**

AE category^a	All patients (advanced solid tumors) N=735	<i>BRCAm</i> ovarian cancer N=397^c
Any AE	718 (97.7)	387 (97.5)
Any AE causally related to study treatment ^b	640 (87.1)	357 (89.9)
Any AE of grade 3 or higher	334(45.4)	189 (47.6)
Any AE with outcome = death	14 (1.9)	10 (2.5)
Any SAE	185 (25.2)	110 (27.7)
Any AE leading to discontinuation of study treatment	43 (5.9)	23 (5.8)

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

b As assessed by the investigator.

c *BRCA* mutation status determined by blood and/or tumor testing.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

AE adverse event; SAE Serious adverse event

Table 41 **Number (%) of patients with the most common AEs - 400 mg bd monotherapy pool**

Preferred term	All patients (advanced solid tumors) N=735	<i>BRCAm</i> ovarian cancer N=397^a
Nausea	459 (62.4)	263 (66.2)
Fatigue	407 (55.4)	233 (58.7)
Vomiting	266 (36.3)	153 (38.5)
Anemia	189 (25.7)	110 (27.7)
Diarrhea	180 (24.5)	113 (28.5)
Abdominal pain	167 (22.7)	103 (25.9)
Decreased appetite	133 (18.1)	69 (17.4)
Headache	132 (18.0)	72 (17.9)
Constipation	119 (16.2)	66 (16.6)

a *BRCA* mutation status determined by blood and/or tumor testing.

Table 42 **Number (%) of patients with the most common AEs of grade ≥ 3 - 400 mg bd monotherapy pool**

System organ class/ Preferred term	All patients (advanced solid tumors) N=735	<i>BRCAm</i> ovarian cancer N=397^a
Any AE of grade ≥ 3	334 (45.4)	189 (47.6)
Blood and lymphatic disorders	116 (15.8)	66 (16.6)
Anemia	84 (11.4)	51 (12.8)
Leukopenia	20 (2.7)	14 (3.5)
Neutropenia	21 (2.9)	13 (3.3)
Thrombocytopenia	16 (2.2)	9 (2.3)
Gastrointestinal disorders	105 (14.3)	64 (16.1)
Abdominal pain	24 (3.3)	16 (4.0)
Intestinal obstruction	15 (2.0)	13 (3.3)
Diarrhea	13 (1.8)	7 (1.8)
Nausea	20 (2.7)	9 (2.3)
Small intestinal obstruction	13 (1.8)	8 (2.0)
Vomiting	24 (3.3)	16 (4.0)
General disorders and administration site conditions	66 (9.0)	38 (9.6)
Fatigue	52 (7.1)	29 (7.3)
Musculoskeletal and connective tissue disorders	25 (3.4)	12 (3.0)
Back pain	6 (0.8)	5 (1.3)
Investigations	42 (5.7)	22 (5.5)
Hemoglobin decreased	17 (2.3)	10 (2.5)
Respiratory, thoracic and mediastinal disorders	31 (4.2)	18 (4.5)
Dyspnea	16 (2.2)	11 (2.8)

^a *BRCA* mutation status determined by blood and/or tumor testing.

Patients with multiple AEs of grade 3 or higher are counted once for each system organ class/preferred term. Data sorted alphabetically by system organ class and preferred term.

Includes AEs with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Table 43 **Number (%) of patients reporting SAEs - Study 19**

System organ class/ Preferred term	Safety Analysis		<i>gBRCAm</i> patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Any SAE	25 (18.4)	11 (8.6)	11 (20.8)	3 (7.0)
Blood and lymphatic system disorders	5 (3.7)	0	1 (1.9)	0
Anemia	3 (2.2)	0	0	0
Pancytopenia ^a	1 (0.7)	0	0	0
Thrombocytopenia ^b	1 (0.7)	0	1 (1.9)	0
Cardiac disorders	1 (0.7)	0	1 (1.9)	0
Cardiovascular insufficiency	1 (0.7)	0	1 (1.9)	0
Gastrointestinal disorders	7 (5.1)	7 (5.5)	2 (3.8)	2 (4.7)
Abdominal pain	0	1 (0.8)	0	0
Constipation	1 (0.7)	0	0	0
Diarrhea	1 (0.7)	0	1 (1.9)	0
Gastritis	0	2 (1.6)	0	1 (2.3)
Impaired gastric emptying	0	1 (0.8)	0	1 (2.3)
Intestinal obstruction	1 (0.7)	1 (0.8)	0	0
Intra-abdominal hemorrhage	1 (0.7)	0	1 (1.9)	0
Melena	1 (0.7)	0	0	0
Small intestinal obstruction	2 (1.5)	3 (2.3)	0	1 (2.3)
Vomiting	1 (0.7)	0	1 (1.9)	0
General disorders & administration site conditions	2 (1.5)	0	2 (3.8)	0
Hernia pain	1 (0.7)	0	1 (1.9)	0
Pyrexia	1 (0.7)	0	1 (1.9)	0
Hepatobiliary disorders	1 (0.7)	0	0	0
Cholestatic jaundice ^c	1 (0.7)	0	0	0
Immune system disorders	1 (0.7)	0	0	0
Iodine allergy	1 (0.7)	0	0	0
Infections and infestations	4 (2.9)	3 (2.3)	4 (7.5)	2 (4.7)
Appendicitis	1 (0.7)	0	1 (1.9)	0
Endophthalmitis	0	1 (0.8)	0	0
Influenza	0	1 (0.8)	0	1 (2.3)

Table 43 **Number (%) of patients reporting SAEs - Study 19**

System organ class/ Preferred term	Safety Analysis		<i>gBRCAm</i> patients	
	Olaparib 400 mg bd N=136	Placebo N=128	Olaparib 400 mg bd N=53	Placebo N=43
Liver abscess	1 (0.7)	0	1 (1.9)	0
Pneumonia	1 (0.7)	1 (0.8)	1 (1.9)	1 (2.3)
Upper respiratory tract infection	1 (0.7)	0	1 (1.9)	0
Urinary tract infection	1 (0.7)	1 (0.8)	1 (1.9)	1 (2.3)
Injury, poisoning and procedural complications	2 (1.5)	0	1 (1.9)	0
Femur fracture ^c	1 (0.7)	0	0	0
Post procedural hematoma	1 (0.7)	0	1 (1.9)	0
Metabolism and nutrition disorders	0	1 (0.8)	0	1 (2.3)
Dehydration	0	1 (0.8)	0	1 (2.3)
Musculoskeletal and connective tissue disorders	1 (0.7)	0	1 (1.9)	0
Osteoporosis	1 (0.7)	0	1 (1.9)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7)	1 (0.8)	0	0
Bladder cancer	0	1 (0.8)	0	0
Breast cancer in situ	1 (0.7)	0	0	0
Nervous system disorders	2 (1.5)	0	1 (1.9)	0
Hemorrhagic stroke ^b	1 (0.7)	0	1 (1.9)	0
Syncope	1 (0.7)	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (2.9)	0	3 (5.7)	0
Cough	1 (0.7)	0	1 (1.9)	0
Dyspnea	2 (1.5)	0	1 (1.9)	0
Pulmonary embolism	1 (0.7)	0	1 (1.9)	0
Vascular disorders	1 (0.7)	1 (0.8)	2 (3.8)	0
Deep vein thrombosis	1 (0.7)	0	1 (1.9)	0
Essential hypertension	0	1 (0.8)	0	0
Vena cava thrombosis	1 (0.7)	0	1 (1.9)	0

a Patient E1801002 who later developed MDS (fatal AE)

b Patient E1808004 who had a fatal AE of hemorrhagic stroke

c Patient E0805001 – cholestatic jaundice recorded as secondary cause of death

Patients reporting multiple SAEs are counted once for each system organ class/preferred term. Data sorted alphabetically by system organ class and preferred term.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Table 44 **Number (%) of patients reported with SAEs ($\geq 0.5\%$ in either group) - 400 mg bd monotherapy pool**

System Organ Class/ Preferred term	All patients (advanced solid tumors) N=735	<i>BRCAm</i> ovarian cancer N=397^a
Any SAE	185 (25.2)	110 (27.7)
Blood and lymphatic system disorders	32 (4.4)	20 (5.0)
Anemia	21 (2.9)	14 (3.5)
Leukopenia	2 (0.3)	2 (0.5)
Neutropenia	4 (0.5)	3 (0.8)
Thrombocytopenia	6 (0.8)	4 (1.0)
Cardiac disorders	6 (0.8)	3 (0.8)
Pericardial effusion	2 (0.3)	2 (0.5)
Gastrointestinal disorders	71 (9.7)	50 (12.6)
Abdominal pain	12 (1.6)	10 (2.5)
Constipation	3 (0.4)	2 (0.5)
Gastrointestinal obstruction	3 (0.4)	3 (0.8)
Ileus	2 (0.3)	2 (0.5)
Intestinal obstruction	14 (1.9)	13 (3.3)
Large intestinal obstruction	2 (0.3)	2 (0.5)
Nausea	8 (1.1)	5 (1.3)
Small intestinal obstruction	14 (1.9)	9 (2.3)
Vomiting	13 (1.8)	9 (2.3)
General disorders and administration site conditions	12 (1.6)	7 (1.8)
Pyrexia	5 (0.7)	3 (0.8)
Infections and infestations	29 (3.9)	20 (5.0)
Bacteremia	2 (0.3)	2 (0.5)
Gastroenteritis	2 (0.3)	2 (0.5)
Infection	3 (0.4)	3 (0.8)
Pneumonia	6 (0.8)	4 (1.0)
Sepsis	3 (0.4)	2 (0.5)
Upper respiratory tract infection	2 (0.3)	2 (0.5)
Urinary tract infection	5 (0.7)	3 (0.8)
Investigations	6 (0.8)	3 (0.8)

Table 44 **Number (%) of patients reported with SAEs (≥0.5% in either group) - 400 mg bd monotherapy pool**

System Organ Class/ Preferred term	All patients (advanced solid tumors) N=735	<i>BRCAm</i> ovarian cancer N=397^a
Decreased hemoglobin	5 (0.7)	3 (0.8)
Metabolism and nutrition disorders	9 (1.2)	4 (1.0)
Dehydration	3 (0.4)	2 (0.5)
Hypokalemia	3 (0.4)	2 (0.5)
Musculoskeletal and connective tissue disorders	10 (1.4)	6 (1.5)
Back pain	2 (0.3)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	25 (3.4)	15 (3.8)
Dyspnea	10 (1.4)	7 (1.8)
Pleural effusion	5 (0.7)	4 (1.0)
Pulmonary embolism	6 (0.8)	4 (1.0)
Vascular disorders	6 (0.8)	4 (1.0)
Deep vein thrombosis	5 (0.7)	3 (0.8)

^a *BRCA* mutation status determined by blood and/or tumor testing.

Sorted alphabetically by SOC and PT. Patients with multiple SAEs are counted once for each SOC/PT.

Includes adverse events with an onset date between the date of first dose and 30 days following the date of last dose of study treatment.

Table 45 **Summary of Patients requiring blood transfusions in Study 19**

Patient number	Day of transfusion(s)	Day study treatment discontinued	Reason for discontinuing study treatment	Number of days patient continued dosing after last transfusion
E0701014	68	204	Disease progression	136
E1202001	69	166	Disease progression	97
E0803006	97	380	Disease progression	283
E0804004	79	336	-	257
E1808004	206	206	Grade 4 leukopenia, neutropenia and thrombocytopenia	0

E0107002	172	174	Disease progression	2
E1801002	305	313	Disease progression (Note: diagnosis f MDS on Day 359)	8
E0701004	57, 89 (2 transfusions)	323	-	234
E1302001	29, 43 (2 transfusions)	257	Disease progression	214
E1303001	80, 86 (2 transfusions)	85	Disease progression	-
E1102004	62, 114 (2 transfusions)	168	Disease progression	54
E1705007	283, 330 (2 transfusions)	395	Disease progression	65
E0701013	115, 123, 142 (3 transfusions)	681	Disease progression	539
E0804006	68, 71 (2 transfusions)	162	Disease progression	91
E0713001	2, 64, 116, 170 (4 transfusions)	-	On placebo	-

Table 46 Number (%) of patients with maximum overall grade during treatment for key clinical chemistry parameters – Study 19

	Safety Analysis		<i>gBRCAm</i> patients	
	Grade ≤2	Grade 3/4	Grade ≤2	Grade 3/4
ALT				
Olaparib 400 mg bd	133/135 (98.5)	2/135 (1.5)	52/53 (98.1)	1/53 (1.9)
Placebo	123/126 (97.6)	3/126 (2.4)	41/42 (97.6)	1/42 (2.4)
AST				
Olaparib 400 mg bd	133/136 (97.8)	3/136 (2.2)	52/53 (98.1)	1/53 (1.9)
Placebo	125/125 (100)	0	42/42 (100)	0
ALP				
Olaparib 400 mg bd	135/136 (99.3)	1/136 (0.7)	52/53 (98.1)	1/53 (1.9)
Placebo	126/126 (100)	0	42/42 (100)	0
Bilirubin				

Table 46 **Number (%) of patients with maximum overall grade during treatment for key clinical chemistry parameters – Study 19**

	Safety Analysis		<i>gBRCAm</i> patients	
	Grade ≤ 2	Grade 3/4	Grade ≤ 2	Grade 3/4
Olaparib 400 mg bd	135/136 (99.3)	1/136 (0.7)	53/53 (100)	0
Placebo	126/127 (99.2)	1/127 (0.8)	43/43 (100)	0
Creatinine				
Olaparib 400 mg bd	134/135 (99.3)	1/135 (0.7)	52/53 (98.1)	1/53 (1.9)
Placebo	127/127 (100)	0	43/43 (100)	0

Table 47 Listing of key information for fatal AEs reported

Study/ patient	Sex/ Age (years)	AE (MedDRA preferred term)	Causally related to olaparib	Time from start of treatment to AE onset (days)	Dose last taken before death (mg)	Time from last dose to death (days)	Time from start of treatment to death (days)
Study 02/ 001-0029	M/51	Lower respiratory tract infection	N	8	200	26	159
Study 02/ 001-0036	F/64	Sepsis	N	29	400	2	30
Study 02/ 001-0057	F/44	Disease progression	Unlikely related	55	200	17	66
Study 02/ 001-0079	F/57	Disease progression	N	94	50	13	109
Study 02/ 001-0081	F/69	Disease progression	N	91	200	20	111
Study 02/ 001-0083	F/39	Intestinal obstruction	N	115	200	24	138
Study 02/ 002-0017	M/67	General physical health deterioration	N	45	60	3	48
Study 02/ 002-0023	M/53	Pulmonary embolism	Unlikely related	30	100	2	30
Study 02/ 002-0044	F/47	Disease progression	N	48	600	23	72
Study 02/ 002-0058	F/65	Disease progression	N	317	200	46	355
Study D9010C00008/ 206027	M/43	Hydronephrosis	N	25	400	31	61
		Pleural effusion	N	60	400	31	61
Study 09/ E0020014	F/69	Congestive cardiac failure	N	64	200	5	68

Table 47 **Listing of key information for fatal AEs reported**

Study/ patient	Sex/ Age (years)	AE (MedDRA preferred term)	Causally related to olaparib	Time from start of treatment to AE onset (days)	Dose last taken before death (mg)	Time from last dose to death (days)	Time from start of treatment to death (days)
Study 09/ E0613005	F/53	Intestinal perforation	N	323	800	2	325
Study 12/ E5005004	F/59	Embolic stroke	Possibly related	17	200	13	27
Study 12/ E7001010	F/71	Myelodysplastic syndrome	Possibly related	152	200	57	183
Study 19/ E0101001	F/63	Acute renal failure		679	800	483	679
Study 19/ E0103005	F/62	Death		671	800	582	671
Study 19/ E0301001	F/65	Pulmonary embolism		428	800	334	428
Study 19/ E0302002	F/55	Euthanasia		1065	400	979	1065
Study 19/ E1002002	F/52	Septic shock		460	800	290	460
Study 19/ E1204002	F/59	Cardiopulmonary failure		890	800	700	890
Study 19/ E1403004	F/50	Cerebrovascular disorder		1002	800	591	1002
Study 19/ E1504003	F/56	Septic shock		811	800	587	811
Study 19/ E1505001	F/77	Cerebral hemorrhage		384	800	214	384
Study 20/ E0104003	F/84	Chronic respiratory failure	N	95	400	0	149

Table 47 **Listing of key information for fatal AEs reported**

Study/ patient	Sex/ Age (years)	AE (MedDRA preferred term)	Causally related to olaparib	Time from start of treatment to AE onset (days)	Dose last taken before death (mg)	Time from last dose to death (days)	Time from start of treatment to death (days)
Study 42/ E0302009	F/63	Acute leukemia	N	37	200	17	205
Study 42/ E2601021	F/41	Enterobacter sepsis	N	227	400	37	264
Study 42/ E2601027	F/56	Pulmonary embolism	N	19	200	1	19
Study 42/ E4001042	F/70	Chronic obstructive pulmonary disease	N	159	400	0	167
Study 42/ E4007006	F/63	Acute myeloid leukemia	N	179	400	79	234
Study 42/ E7001005	F/49	Suture rupture	N	117	200	15	121
Study 42/ E7201003	F/58	Cerebrovascular accident	N	78	400	8	91

Table 48 Details of reported MDS/AML events (DCO 02 May 2014)

Study	Patient identifier/ Age/ Patient safety database ID	Cancer under treatment/ Year of diagnosis	Study treatment received	Days on study treatment	Diagnosis relative to end of olaparib treatment	BRCA mutation status	AE as reported term by the investigator	Prior chemotherapy received	Previous agents received including radiotherapy	Previous cancer	MDS/AML Outcome
MDS/AML events in olaparib treated patients											
Study 19 Phase II maintenance study	E1801002 ^a /77/2010SE20903	Primary peritoneal/2007	Olaparib 400 mg bd	313	Whilst on treatment	Wildtype	MDS	2 regimens over 2 years	Carboplatin, paclitaxel, gemcitabine	Malignant melanoma 1997	Died due to 1. Ovarian cancer 2. MDS
	E0801001/53/2014SE00318	Ovarian/2007	Olaparib 400 mg bd	1728	+21 days	<i>BRCAm</i>	AML	2 regimens over 2 years	Carboplatin, paclitaxel x2	No	Ongoing
Study 41 Phase II combination followed by maintenance	E1405004/78/2012SE01112	Ovarian/2009	O/C4/P (6 cycles) followed by olaparib	547	Whilst on treatment	Wildtype	MDS	6 cycles over 4 months (1 regimen) plus O/C4/P regimen as part of the study	Carboplatin, paclitaxel	No	Died due to 1. cerebral haemorrhage 2. DIC
	E1503001/61/2012SE55581	Ovarian/2001	O/C4/P (6 cycles) followed by olaparib	805	+ 4 days	<i>BRCAm</i>	MDS	3 regimens over 7 years plus O/C4/P regimen as part of the study	Carboplatin, paclitaxel	No	Died due to MDS
Study 12 <i>gBRCA</i> monotherapy dose finding study	E7001010 ^a /71/2009AP01133	Ovarian/1996	Olaparib 200 mg bd	126	+ 26 days	<i>BRCAm</i>	Unclassifiable MDS	Multiple regimens over 12 years	Carboplatin, paclitaxel, adriamycin, marimastat, cisplatin	No	Died due to MDS
	E6007014 ^a /63/2010SE49560	Fallopian tubes/2005	Olaparib 200 mg bd	744	Whilst on treatment	<i>BRCAm</i>	1. MDS 2. AML	4 regimens over 17 years	Doxorubicin, cyclophosphamide, adriamycin, paclitaxel, carboplatin, docetaxel, radiotherapy ^b	Breast	Died due to complication of double umbilical cord blood transplantation (dUCBT)

Table 48 **Details of reported MDS/AML events (DCO 02 May 2014)**

Study	Patient identifier/ Age/ Patient safety database ID	Cancer under treatment/ Year of diagnosis	Study treatment received	Days on study treatment	Diagnosis relative to end of olaparib treatment	<i>BRCA</i> mutation status	AE as reported term by the investigator	Prior chemotherapy received	Previous agents received including radiotherapy	Previous cancer	MDS/AML Outcome
Study 42 Advanced g <i>BRCA</i> cancers	E0302009 ^a /63/ 2011SE06200	Peritoneum/ 2007	Olaparib 400 mg bd	188	Whilst on treatment. Pre-existing MDS present at baseline	<i>BRCAm</i>	Worsening myelodysplasia leading to acute leukaemia	Multiple regimens over 15 years	Cyclophosphamide, methotrexate, epirubicin, carboplatin, paclitaxel, gemcitabine, liposomal doxorubicin, radiotherapy ^b	Breast 1995	Died due to 1. Acute leukaemia. 2. MDS
	E4007006 /63/ 2011SE44481	Ovarian/ 2007	Olaparib 400 mg bd	155	+ 24 days	<i>BRCAm</i>	AML	4 regimens over 3 years	Carboplatin, cisplatin, paclitaxel	No	Died due to 1. Acute myeloid leukaemia 2. Ovarian cancer
	E4003003 /45/ 2012SE04128	Ovarian/ 2005	Olaparib 400 mg bd	298	+ 298 days	<i>BRCAm</i>	MDS unspecified	3 regimens over 5 years	Cytosan, cisplatin, carboplatin, radiotherapy	No	Died due to 1. Multi-organ disorder 2. MDS
	E7802029 ^a /61/ 2013SE25706	Peritoneum / 2007	Olaparib 400 mg bd	764	+ 23 days	<i>BRCAm</i>	1.MDS 2.AML	At least 4 regimens over 3 years	Carboplatin, paclitaxel, bevacizumab, topotecan ^b	Breast; basal cell cancer	Died due to acute myelogenous leukaemia
	E7802003 /55/ 2011SE33446	Ovarian/ 2006	Olaparib 400 mg bd	152	+ 379 days	<i>BRCAm</i>	MDS	5 regimens over 4 years	Carboplatin, docetaxel, paclitaxel, cyclophosphamide, gemcitabine	No	Died due to ovarian cancer

Table 48 **Details of reported MDS/AML events (DCO 02 May 2014)**

Study	Patient identifier/ Age/ Patient safety database ID	Cancer under treatment/ Year of diagnosis	Study treatment received	Days on study treatment	Diagnosis relative to end of olaparib treatment	BRCA mutation status	AE as reported term by the investigator	Prior chemotherapy received	Previous agents received including radiotherapy	Previous cancer	MDS/AML Outcome
	E4001012 /51/ 2013SE75867	Breast / 2007	Olaparib 400 mg bd	1251	Whilst on treatment	<i>BRCA1m</i>	MDS	3 regimens over 2 years 2 months (breast) + 1 regimen 4 years earlier for ovarian cancer	Carboplatin, and paclitaxel; Cyclophosphamide + doxorubicin + fluouracil; cisplatin and gemcitabine ^b	Ovarian	Ongoing
Study 02 First time in human study	001-0078 ^a /70/ 2010SE31079	Ovarian/ 2002	Olaparib 200 mg bd	981	Whilst on treatment	<i>BRCAm</i>	Myelodysplasia	4-5 regimens over 10 years	Cyclophosphamide, 5FU, methotrexate, carboplatin, paclitaxel, radiotherapy ^b	Breast	Died due to AML
Study 09 <i>gBRCA</i> ovarian proof of concept study	E0017011 /68/ NA	Ovarian/ 2004	Olaparib 400 mg bd	231	+ 265 days	<i>BRCAm</i>	Not reported as AE	21 cycles over 3 years (multiple regimens)	Carboplatin, paclitaxel, cisplatin, topotecan ^b	Breast	Died due to AML
	E0613008 /63/ 2012SE43381	Ovarian/ 2006	Olaparib 400 mg bd	1759	Whilst on treatment	<i>BRCAm</i>	Myelodysplasia converted to AML	2 regimens over 1 year	Cisplatin, paclitaxel, pazopanib	No	Died due to AML
Study 98 Investigator sponsored study	8348038/ 67/ 2013SE12306	Ovarian/ 2008	Cediranib + olaparib 200 mg bd	373	+ 45 days	Not available	MDS	19 cycles over 9 months	Carboplatin, cisplatin, gemcitabine, iniparib, paclitaxel	No	Died due to ovarian cancer
Study 59 Investigator sponsored study	008 ^a / 60/ 2013SE17724	Ovarian/ 2007	Carboplatin/ paclitaxel/ olaparib	91	Whilst on treatment	Not available	MDS	7 regimens over 4 years	Carboplatin, paclitaxel, bevacizumab, adriamycin	No	Ongoing

Table 48 **Details of reported MDS/AML events (DCO 02 May 2014)**

Study	Patient identifier/ Age/ Patient safety database ID	Cancer under treatment/ Year of diagnosis	Study treatment received	Days on study treatment	Diagnosis relative to end of olaparib treatment	BRCA mutation status	AE as reported term by the investigator	Prior chemotherapy received	Previous agents received including radiotherapy	Previous cancer	MDS/AML Outcome
Study 04 Combination dose-finding study	2117/ 64/ 2012SE27737	Ovarian/ 2006	Olaparib 100 mg tablet bd/ carboplatin AUC4/ paclitaxel	580	+19 days	<i>BRCAm</i>	Myelodysplasia	1 regimen over 6 months	Carboplatin, paclitaxel, radiotherapy ^b	Breast	Died due to MDS
Study 24 Bioavailability study	E0008004 /50/ 2013SE42706	Ovarian/ 2002	Olaparib 400 mg bd	735	Whilst on treatment	<i>BRCA1m</i>	MDS	4 regimens over 7 years	Carboplatin and paclitaxel x3 Liposomal doxorubicin	No	Died (MDS, hematuria, respiratory failure)
Study 55 Pancreatic study	JH001/ 67/ 2013SE84473	Pancreas/ 2011	Olaparib, irinotecan, cisplatin (varying dose levels)	693	Whilst on treatment	<i>BRCAm</i>	MDS	Not stated	capecitabine and radiation therapy	No	Ongoing
	JH004/ 67/ 2013SE84496	Pancreas/ 2007 (imputed)	Olaparib, irinotecan, cisplatin (varying dose levels)	343	+220 days	Not stated	MDS	yes	Gemcitabine, capecitabine, and radiotherapy	No	Ongoing
MDS/AML events in placebo/control arm patients											
Study 19 Phase II maintenance study	E0805002 /71/ NA	Ovarian/ 2003	Placebo	1128	Whilst on treatment	Tumor <i>BRCAm</i>	MDS	2 regimens over 6 years	carboplatin	No	Ongoing

Table 48 **Details of reported MDS/AML events (DCO 02 May 2014)**

Study	Patient identifier/ Age/ Patient safety database ID	Cancer under treatment/ Year of diagnosis	Study treatment received	Days on study treatment	Diagnosis relative to end of olaparib treatment	BRCA mutation status	AE as reported term by the investigator	Prior chemotherapy received	Previous agents received including radiotherapy	Previous cancer	MDS/AML Outcome
Study 12 <i>gBRCA</i> monotherapy dose finding study	E8001092 /59/ NA	Ovarian/ 2004	PLD	197	N/A	<i>BRCAm</i>	Not reported as AE	18 cycles over 3.5 years (2 regimens)	Carboplatin, paclitaxel, docetaxel	No	Died due to 1. Sepsis 2. MDS

Information taken from the Clinical Database and AstraZeneca Patient Safety Database.

a Patients with abnormalities of chromosomes 5, 7 and/or complex karyotypes

b Chemotherapy data for cancer prior to disease treated with olaparib is limited therefore cancer therapy history as reported overall will be underestimated.